CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-436

CHEMISTRY REVIEW(S)
Chemistry Review Data Sheet

1. NDA 21-436
2. REVIEW # 2
3. REVIEW DATE: 8/28/02
4. REVIEWER: Sherita McLamore, Ph.D.
5. PREVIOUS DOCUMENTS:

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<td>6/24/02</td>
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7. NAME & ADDRESS OF APPLICANT:

Name: Otsuka Pharmaceuticals Company, Ltd
2-9 Kanda Tsukasa-cho
Address: Chiyoda-Ku Tokyo
101-8535, Japan
Representative: Dr. Gary Ingenito
Telephone: 203.677.6674

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Abilitat (not accepted)
b) Non-Proprietary Name / USAN [1997]: 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: Immediate Release Tablet

12. STRENGTH/POTENCY: 2, 5, 10, 15, 20 and 30 mg/tablet

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: __X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note24]:
   - ___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:
Number of Pages Redacted

Confidential, Commercial Information
Chemistry Assessment Section

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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")

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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The Chemistry Review for NDA 21-436

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability
   The Chemistry, Manufacturing, and Controls (CMC) section of NDA 21-436 is not approvable because of the cGMP issues with respect to the drug product manufacturing site (withheld recommendation). The applicant will be sent a list of deficiencies in the FDA Action Letter.

   Methods validation will be submitted after all CMC issues 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. The drug substance is a new molecular entity and accordingly the applicant claims exclusivity for the drug product.

   Aripiprazole was originally investigated under IND ___________ In 1999, the applicant, Otsuka Pharmaceuticals and Bristol-Myers Squibb entered into a collaborative agreement to market the drug product. Aripiprazole tablets are available in 2, 5, 10, 15, 20 and 30 mg strengths. Originally, the 20 and 30 mg tablet were formulated to be proportionally similar to the 15 mg tablets. However, this formulation resulted in slow and incomplete dissolution. Consequently, to improve dissolution, the applicant redesigned the 20 and 30 mg tablets. The formulation for the 20 and 30 mg tablets are proportionally similar to the 10 mg tablets. This new formulation exhibited a markedly improved dissolution.

   The applicant indicates that the drug product will be manufactured at the Bristol Myers Squibb facility in Mayaguez, Puerto Rico or at the Otsuka Pharmaceutical facility in Tokushima, Japan. The 2 mg dosage is a green, modified rectangular shape tablet with “A-006” and “2” debossed on one side and scored on the other. The 5 mg dosage is a blue, modified rectangular shape tablet with “A-007” and “5” debossed on one side and scored on the other. The 10 mg
dosage is a pink, modified rectangular shape tablet with "A-008" and "10" debossed on one side. The 15 mg dosage is a yellow, round tablet with "A-009" and "15" debossed on one side. The 20 mg dosage is a white to pale yellowish white, round tablet with "A-010" and "20" debossed on one side. The 30 mg dosage is a pink, round tablet with "A-011" and "30" debossed on one side. The tablet weights of the 2, 5, 10, and 15 mg tablets are 95.0 mg. The 20 and 30 mg tablets are 189.76 mg and 285.0 mg, respectively. Each of the six strengths are packaged in 95 and 200-cc square, white opaque HDPE bottles, induction heat sealed and capped with a closure. The closures for the 95 and 200 cc bottles are child resistant and non child resistant, respectively. Additionally, each of the six strengths are packaged in aluminum/aluminum cold-form blisters.

The applicant includes detailed information on the drug substance in this application. The drug substance is described as a white crystalline powder with a melting point of 139.3°C. The molecular formula for the drug substance is C_{23}H_{27}Cl_{2}N_{5}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 applicant proposed the proprietary name ABILITAT™ for the drug product. The Office of Post–Marketing Drug Risk Assessment (OPDRA) does not recommend the use of ABILITAT based on the information that is currently available.

B. Description of How the Drug Product is Intended to be Used
Aripiprazole Tablets are being developed for the treatment of schizophrenia. The recommended starting dose is 15 mg once a day. The applicant indicates that there is no available data that suggest doses higher than 15 mg QD are more efficacious. The 30 mg QD has been established as an effective dose and was the highest dose systematically evaluated in the clinical trials.

The applicant has requested a 24 month shelf life for all potencies of Aripiprazole Tablets in bottles and blisters (V 1.5, page 1). As indicated in the stability section of this review, the
applicant provided up to 18 months of primary stability data for the 2-, 5-, 10-, and 15 mg tablets and 6 months of data for the 20 and 30 mg tablets from the Japanese site and 6 months of data for one batch each of the 20 and 30 mg tablets from the Puerto Rico site. The applicant also included certificates of analyses for the 5, 10, 15, 20 and 30 mg tablets manufactured at the Puerto Rico facility.

In light of the dissolution problems at the Mayaguez, Puerto Rico facility (see page 57 of this review), the limited amount of stability data available from the Mayaguez, Puerto Rico facility and the apparent limited amount of data available for the current formulations of the 20 and 30 mg tablets, we will not set an expiry for the drug product at this time. Moreover, the applicant has not provided adequate data to support the manufacture of the 2 mg tablets at the Mayaguez, Puerto Rico facility.

C. Basis for Approvability or Not-Approval Recommendation

NDA 21-436 is Not Approvable from the chemistry, manufacturing and controls (CMC) standpoint. The "Not Approvable" recommendation is based on the following:

- Withhold recommendation from the FDA’s Office of Compliance regarding cGMP status of Britol’s Mayaguez, PR site (CFN #2627673). This site was submitted as a manufacturer, packager, and release tester of the drug product.

- Other CMC concerns related to the drug substance and drug product sections as outlined in Chemistry Review #1 by Dr. Sherita McLamore. These deficiencies outlined in Chemistry Review #1 constitute an APPROVABLE recommendation from the CMC standpoint.

Before NDA 21-436 can be approved for CMC, the proposed site for drug product manufacturing, packaging and release testing (CFN #2627673) should receive an acceptable recommendation from the Office of Compliance and the CMC issues (outlined in Review #1) be properly addressed. Alternatively, because two sites were submitted for the manufacturing, packaging and release testing of the drug product, the applicant can withdraw the BMS Mayaguez, Puerto Rico facility (CFN 2627673) from their application.

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

SMC McLamore/Date
TOL Oliver (TL)/Date
C. CC Block
   Orig. NDA 21-436
   HFD-120/Division File
   HFD-120/SHardeman
   HFD-120/SMcLamore
   HFD-120/TOliver
THIS SECTION WAS DETERMINED NOT TO BE RELEASABLE

2 pages
CHEMISTRY REVIEW TEMPLATE

Chemistry Assessment Section

27-AUG-2002

FDA CDER RDS
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 21436/000
Org Code: 120
Priority: 18

Sponsor: OTSUKA PHARM

Stamp Date: 31-OCT-2001
FDUPA Date: 31-AUG-2002
Action Goal: 02-JUL-2002
District Goal: 02-JUL-2002

Brand Name: ABILITAT (ARIPIPRAZOLE)
Estab. Name: GENERIC

FDA Contacts:

S. HARDMAN
Project Manager (HPD-120) 301-594-2850
S. MCLAMORE
Review Chemist (HPD-810) 301-594-5359
T. OLIVER
Team Leader (HPD-810) 301-594-2970

Overall Recommendation: WITHHOLD on 23-AUG-2002 by B. HARTMAN (HPD-120) 301-827-0089

Establishment:

DMF No:

Responsible:

Profile: TCM
Last Milestone: OC RECOMMENDATION
Milestone Date: 26-NOV-01
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment: CFN: 2627673 FBI: 2627673
BRISTOL LABORATORIES INC DIV BRISTOL MYERS CO
FOREIGN TRADE ZONE 7 RD 114
MAYAGUEZ, PR 00680

DMF No: AADA:

Responsibilities:

FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER

Profile: TCM
Last Milestone: OC RECOMMENDATION
Milestone Date: 23-AUG-02
Decision: WITHHOLD
Reason: BBR REVIEW-CONCUR w/DISTRICT

Establishment: CFN: 1819504 FBI: 1819504
BRISTOL MYERS SQUIBB CO
2400 WEST LLOYD EXY
EVANSVILLE, IN 477210001

DMF No: AADA:
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Establishment: CPW: 1825662  
PHI: 1825663  
BRISTOL MYERS SQUIBB CO  
ENY 62 WEST BLDG 122  
MOUNT VERNON, IN 47620  

DMF No: AADA  

| Responsibilities: | FINISHED DOSAGE PACKAGER  |
| Profile: | TCM  |
| Last Milestone: | OC RECOMMENDATION  |
| Milestone Date: | 26-NOV-01  |
| Decision: | ACCEPTABLE  |
| Reason: | BASED ON PROFILE  |

Establishment:  

DMF No:  

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| Decision: | ACCEPTABLE  |
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| Milestone Date: | 29-NOV-01  |
| Decision: | ACCEPTABLE  |
| Reason: | DISTRICT RECOMMENDATION  |

Establishment: CPW:  
PHI:  

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### Chemistry Review Template

#### Chemistry Assessment Section

**27-AUG-2002**

**FDA CDER ESS**

**ESTABLISHMENT EVALUATION REQUEST**

**SUMMARY REPORT**

**OTSUKA PHARMACEUTICAL CO LTD**

**MATSUTANI ITANO-CHO ITANO-GUN**

**TOKUSHIMA, JA**

**DMF No:** AADA

**Responsibilities:**

- FINISHED DOSAGE MANUFACTURER
- FINISHED DOSAGE TESTER
- FINISHED DOSAGE STABILITY TESTER

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**Milestone Date:** 19-JUL-02

**Decision:** ACCEPTABLE

**Reason:** DISTRICT RECOMMENDATION

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**Establishment:**

**CEN:** 9611255

**FBI:** 3002807834

**OTSUKA PHARMACEUTICAL CO LTD, SECOND TOKUSHIMA FACTORY**

**KAMACHI-CHO (2ND TOKUSHIMA), TOKUSHIMA, JA**

**DMF No:** AADA

**Responsibilities:**

- DRUG SUBSTANCE MANUFACTURER
- DRUG SUBSTANCE PACKAGER
- DRUG SUBSTANCE RELEASE TESTER
- DRUG SUBSTANCE STABILITY TESTER

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**Milestone Date:** 09-JUL-02

**Decision:** ACCEPTABLE

**Reason:** DISTRICT RECOMMENDATION

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**Last Milestone:** OC RECOMMENDATION

**Milestone Date:** 26-NOV-01

**Decision:** ACCEPTABLE

**Reason:** BASED ON PROFILE
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
8/28/02 09:41:40 AM
CHEMIST

Thomas Oliver
8/28/02 12:35:10 PM
CHEMIST

APPEARS THIS WAY
ON ORIGINAL
NDA 21-436

Aripiprazole Tablets

Otsuka Pharmaceuticals Company, Ltd

Sherita D. McLamore, Ph.D.
HFD-120
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Chemistry Review Data Sheet

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3. REVIEW DATE: 8/1/02
4. REVIEWER: Sherita McLamore, Ph.D.
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12. STRENGTH/POTENCY: 2, 5, 10, 15, 20 and 30 mg/tablet

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___SPOTS product – Form Completed

_X_Not a SPOTS product

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Molecular Formula: C_{23}H_{27}Cl_{2}N_{3}O_{2}
Molecular Weight: 448.38
THIS SECTION WAS NOT DETERMINED TO BE releasable
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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18. STATUS:

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<tr>
<td>Methods Validation</td>
<td>Pending</td>
<td>Pending</td>
<td>Sherita McLamore, Ph.D.</td>
</tr>
</tbody>
</table>
The Chemistry Review for NDA 21-436

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability
   The Chemistry, Manufacturing, and Controls (CMC) section of NDA 21-436 is approvable. The applicant will be sent a list of 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. The drug substance is a new molecular entity and accordingly the applicant claims exclusivity for the drug product.

Aripiprazole was originally investigated under __________ in 1993. In 1999, the applicant, Otsuka Pharmaceuticals and Bristol-Myers Squibb entered into a collaborative agreement to market the drug product. Aripiprazole tablets are available in 2, 5, 10, 15, 20 and 30 mg strengths. Originally, the 20 and 30 mg tablet were formulated to be proportionally similar to the 15-mg tablets. However, this formulation resulted in slow and incomplete dissolution. Consequently, to improve dissolution, the applicant redesigned the 20 and 30 mg tablets. The formulation for the 20 and 30 mg tablets are proportionally similar to the 10 mg tablets. This new formulation exhibited a markedly improved dissolution.

The applicant indicates that the drug product will be manufactured at the Bristol Myers Squibb facility in Mayaguez, Puerto Rico or at the Otsuka Pharmaceutical facility in Tokushima, Japan. The 2 mg dosage is a green, modified rectangular shape tablet with “A-006” and “2” debossed on one side and scored on the other. The 5 mg dosage is a blue, modified rectangular
shape tablet with “A-007” and “5” debossed on one side and scored on the other. The 10 mg dosage is a pink, modified rectangular shape tablet with “A-008” and “10” debossed on one side. The 15 mg dosage is a yellow, round tablet with “A-009” and “15” debossed on one side. The 20 mg dosage is a white to pale yellowish white, round tablet with “A-010” and “20” debossed on one side. The 30 mg dosage is a pink, round tablet with “A-011” and “30” debossed on one side. The tablet weights of the 2, 5, 10, and 15 mg tablets are 95.0 mg. The 20 and 30 mg tablets are 189.76 mg and 285.0 mg, respectively. Each of the six strengths are packaged in 95 and 200-cc square, white opaque HDPE bottles, induction heat sealed and capped with a closure. The closures for the 95 and 200 cc bottles are child resistant and non child resistant, respectively. Additionally, each of the six strengths are packaged in aluminum/aluminum cold-form blisters.

The applicant includes detailed information on the drug substance in this application. The drug substance is described as a white crystalline powder with a melting point of 139.3°C. The molecular formula for the drug substance is C_{23}H_{27}ClL_{3}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 applicant proposed the proprietary name ABILITAT™ for the drug product. The Office of Post–Marketing Drug Risk Assessment (OPDRA) does not recommend the use of ABILITAT based on the information that is currently available.

B. Description of How the Drug Product is Intended to be Used
Aripiprazole Tablets are being developed for the treatment of schizophrenia. The recommended starting dose is 15 mg once a day. The applicant indicates that there is no available data that suggest doses higher than 15 mg QD are more efficacious. The 30 mg QD has been established as an effective dose and was the highest dose systematically evaluated in the clinical trials.
The applicant has requested a 24 month shelf life for all potencies of Aripiprazole Tablets in bottles and blisters (V 1.5, page 1). As indicated in the stability section of this review, the applicant provided up to 18 months of primary stability data for the 2-, 5-, 10-, and 15 mg tablets and 6 months of data for the 20 and 30 mg tablets from the Japanese site and 6 months of data for one batch each of the 20 and 30 mg tablets form the Puerto Rico site. The applicant also included certificates of analyses for the 5, 10, 15, 20 and 30 mg tablets manufactured at the Puerto Rico facility.

In light of the dissolution problems at the Mayaguez, Puerto Rico facility (see page 57 of this review), the limited amount of stability data available from the Mayaguez, Puerto Rico facility and the apparent limited amount of data available for the current formulations of the 20 and 30 mg tablets, we will not set an expiry for the drug product at this time. Moreover, the applicant has not provide adequate data to support the manufacture of the 2 mg tablets at the Mayaguez, Puerto Rico facility.

C. Basis for Approvability or Not-Approval Recommendation
NDA 21-436 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 21-436
HFD-120/Division File
HFD-120/SHardeman
HFD-120/SMcLamore
HFD-120/TOLiver
Establishment:  

Responsibilities: FINISHED DOSAGE PACKAGER
Profile: TCM  
Last Milestone: OC RECOMMENDATION
Milestone Date: 26-NOV-01
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment:  

Responsibilities: FINISHED DOSAGE PACKAGER
Profile: TCM  
Last Milestone: OC RECOMMENDATION
Milestone Date: 26-NOV-01
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment:  

Responsibilities: FINISHED DOSAGE PACKAGER
Profile: TCM  
Last Milestone: OC RECOMMENDATION
Milestone Date: 26-NOV-01
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment:  

Responsibilities: FINISHED DOSAGE PACKAGER
Profile: TCM  
Last Milestone: OC RECOMMENDATION
Milestone Date: 26-NOV-01
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment:  

Responsibilities:
CHEMISTRY REVIEW TEMPLATE

Chemistry Assessment Section

30-JUL-2002

FDA CDER EES

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

OTSUKA PHARMACEUTICAL CO LTD
MATSUTANI ITANO-CHO ITANO-GUN
TOKUSHIMA, JA

DMF No: AADA:

Responsibilities:
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE OTHER TESTER
FINISHED DOSAGE STABILITY TESTER

Profile: CTL
OAI Status: NONE

Last Milestone: OC RECOMMENDATION
Milestone Date: 19-JUL-02
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Profile: TCM
OAI Status: NONE

Last Milestone: OC RECOMMENDATION
Milestone Date: 19-JUL-02
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment:

CPN: 9611255
FRN: 3002807834
OTSUKA PHARMACEUTICAL CO LTD, SECOND TOKUSHIMA FACTORY
KANASHI-CHO (2ND TOKUSHIMA), TOKUSHIMA, JA

DMF No: AADA:

Responsibilities:
DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE PACKAGER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER

Profile: CSN
OAI Status: NONE

Last Milestone: OC RECOMMENDATION
Milestone Date: 09-JUL-02
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment:

DMF No: __________

Responsibilities:

Profile: TCM
OAI Status: NONE

Last Milestone: OC RECOMMENDATION
Milestone Date: 26-NOV-01
Decision: ACCEPTABLE
Reason: BASED ON PROFILE
Chemistry Assessment Section

APPEARS THIS WAY
ON ORIGINAL
THIS SECTION WAS DETERMINED NOT TO BE RELEASABLE

2 pages
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
8/13/02 01:04:19 PM
CHEMIST

Thomas Oliver
8/13/02 01:45:12 PM
CHEMIST

APPEARS THIS WAY
ON ORIGINAL
NDA 21-436

Aripiprazole Tablets

Otsuka Pharmaceuticals Company, Ltd

Sherita D. McLamore, Ph.D.
HFD-120
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Chemistry Review Data Sheet

1. NDA 21-436

2. REVIEW # 2

3. REVIEW DATE: 10/11/02

4. REVIEWER: Sherita McLamore, Ph.D.

5. PREVIOUS DOCUMENTS:

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<td>9/18/02</td>
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<tr>
<td>Amendment</td>
<td>10/03/02</td>
</tr>
</tbody>
</table>

7. NAME & ADDRESS OF APPLICANT:

| Name: Otsuka Pharmaceuticals Company, Ltd                    |               |
| 2-9 Kanda Tsukasa-cho                                       |               |
| Address: Chiyoda-Ku Tokyo                                   |               |
| 101-8535, Japan                                             |               |
| Representative: Dr. Gary Ingenito                          |               |
| Telephone: 203.677.6674                                     |               |

8. DRUG PRODUCT NAME/CODE/TYPE:
a) Proprietary Name: Abilatit (not accepted)
b) Non-Proprietary Name / USAN [1997]: 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: Immediate Release Tablet

12. STRENGTH/POTENCY: 2, 5, 10, 15, 20 and 30 mg/tablet

13. ROUTE OF ADMINISTRATION: oral

14. Rx/OTC DISPENSED: _X_Rx _____OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note24]:

   _____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-dihydro2(1H)-quinolinone
   Molecular Formula: C_{23}H_{27}Cl_{2}N_{3}O_{2}
   Molecular Weight: 448.39

![Chemical Structure Diagram]
1. Action codes for DMF Table:
   1 – DMF Reviewed.
   Other codes indicate why the DMF was not reviewed, as follows:
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   3 – Reviewed previously and no revision since last review
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<td>Pending</td>
<td>Sherita McLamore, Ph.D.</td>
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</table>
The Chemistry Review for NDA 21-436

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability
   From a Chemistry, Manufacturing, and Controls (CMC) perspective, it is recommended that NDA 21-436 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. The drug substance is a new molecular entity and accordingly the applicant claims exclusivity for the drug product.

Aripiprazole was originally investigated under in 1993. In 1999, the applicant, Otsuka Pharmaceuticals and Bristol-Myers Squibb entered into a collaborative agreement to market the drug product. Aripiprazole tablets are available in 2, 5, 10, 15, 20 and 30 mg strengths. Originally, the 20 and 30 mg tablet were formulated to be proportionally similar to the 15 mg tablets. However, this formulation resulted in slow and incomplete dissolution. Consequently, to improve dissolution, the applicant redesigned the 20 and 30 mg tablets. The formulation for the 20 and 30 mg tablets are proportionally similar to the 10 mg tablets. This new formulation exhibited a markedly improved dissolution.

The applicant indicates that the drug product will be manufactured at the Bristol Myers Squibb facility in Mayaguez, Puerto Rico or at the Otsuka Pharmaceutical facility in Tokushima, Japan. The 2 mg dosage is a green, modified rectangular shape tablet with “A-006” and “2” debossed on one side and scored on the other. The 5 mg dosage is a blue, modified rectangular shape tablet with “A-007” and “5” debossed on one side and scored on the other. The 10 mg dosage is a pink, modified rectangular shape tablet with “A-008” and “10” debossed on one
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The applicant includes detailed information on the drug substance in this application. The drug substance is described as a white crystalline powder with a melting point of 139.3°C. The molecular formula for the drug substance is C_{22}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.

Initially, the applicant proposed the proprietary name ABILITAT™ for the drug product. The Office of Post-Marketing Drug Risk Assessment (OPDRA) does not recommend the use of ABILITAT based on the information that is currently available. The applicant later proposed the name Abilify. The Division of Medication Errors and Technical Support (DMETS) indicated that there were no objections to the use of Abilify as the proprietary name for Aripiprazole Tablets.

B. Description of How the Drug Product is Intended to be Used
Aripiprazole Tablets are being developed for the treatment of schizophrenia. The recommended starting dose is 15 mg once a day. The applicant indicates that there is no available data that suggest doses higher than 15 mg QD are more efficacious. The 30 mg QD has been established as an effective dose and was the highest dose systematically evaluated in the clinical trials.
The applicant included 18 months of primary stability data for the 2-, 5-, 10-, and 15 mg tablets and 6 months of data for the 20 and 30 mg tablets from the Japanese site. In addition to the data submitted from the Japanese site, the applicant included a limited amount of data from the site in Mayaguez, Puerto Rico (CFN 2627673). Upon inspection, the site in Puerto Rico was found unacceptable by the Office of Compliance. As a result, the overall recommendation from OC of withhold was issued for the application. To circumvent this problem, the applicant withdrew the site from the application.

The applicant has requested expiration dating for all potencies of Aripiprazole Tablets in bottles and blisters (amendment dated 5/31/02). The applicant has not provided adequate stability data to Based on the stability data included in this application, the applicant will be granted a 24 month shelf life for all potencies of the drug product.

C. Basis for Approvability or Not-Approval Recommendation
NDA 21-436 is Approved from the Chemistry standpoint. There are no outstanding chemistry, manufacturing and controls issues related to this application.

III. Administrative

A. Reviewer’s Signature

B. Endorsement Block
SMcLamore/Date
TOLiver (TL)/Date
SHardeman (PM)/Date

C. CC Block
Orig. NDA 21-436
HFD-120/Division File
HFD-120/SHardeman
HFD-120/SMcLamore
HFD-120/TOLiver
THIS SECTION WAS DETERMINED NOT TO BE RELEASABLE
Bristol-Myers Squibb
Pharmaceutical Research Institute
Richard L. Geelhoed Center for Pharmaceutical Research and Development
5 Research Parkway P.O. Box 500 Wallingford, CT 06492-5660
October 3, 2002

Russell Katz, M.D., Director
Division of Neuropharmacologic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
Attention: Division Document Control Room 4008
HFD-120
Woodmont II Building
1451 Rockville Pike
Rockville, MD 20852

Dear Dr. Katz:

Reference is made to NDA No. 21-436 for ABILIFY™ (aripiprazole) tablets, which was submitted on October 31, 2001. Additional reference is made to the Agency's approvable letter for this NDA dated August 29, 2002 and our September 18, 2002 response to the approvable letter.

As noted in the Agency's approvable letter, the Bristol drug product manufacturing, packaging, and release testing facility located in Mayaguez, PR (CFN #2627673) was found to be unacceptable by the FDA's Office of Compliance and a satisfactory inspection will be needed if we plan to use this facility for production of Abilify. The purpose of this submission is to notify the Agency of our decision to withdraw the Mayaguez, PR facility from the NDA at this time, without prejudice to refiling the site at a later date, post NDA approval. As noted in the approvable letter, the NDA contains an accepted alternate site of manufacturing, Otsuka, Japan's Ibaraki manufacturing site, which will supply tablets for the US market.

If there are any additional questions or concerns regarding this submission, please call me at 203-677-6674.

Sincerely,

[Signature]

Charles D. Wolleben, Ph.D.
Director, Regulatory Science
08-OCT-2002

FDA CDER RES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 21436/000
Org Code: 120
Priority: 15

Stamp Date: 31-OCT-2001
PDUFA Date: 19-NOV-2002
Action Goal:
District Goal: 02-JUL-2002

Brand Name: ABILITAT (ARIPIPRAZOLE)
Generic Name: ARIPIPRAZOLE
Dosage Form: (TABLET)
Strength: 2, 5, 10, 15, 20, 30 MG

FDA Contacts:
S. HARDMAN Project Manager (HPD-120) 301-594-2850
S. McLAME Review Chemist (HPD-810) 301-594-5359
T. OLIVER Team Leader (HPD-810) 301-594-2570

Overall Recommendation: ACCEPTABLE on 07-OCT-2002 by J. DAMBROGIO (HPD-324) 301-827-0062
WITHHELD on 23-AUG-2002 by R. HARTMAN (HPD-324) 301-827-0067

Establishment:

DMF No:

Responsibilities:
Profile: TCM OAI Status: NONE

Last Milestone: OC RECOMMENDATION
Milestone Date: 26-NOV-01
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment: CFN: 1819504 FEI: 1819504
BRISTOL MYERS SQUIBB CO
2400 WEST LLOYD EXPY
EVANSVILLE, IN 477200001

Responsibilities: FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile: TCM OAI Status: NONE

Last Milestone: OC RECOMMENDATION
Milestone Date: 26-NOV-01
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment: CFN: 1825662 FEI: 1825662
BRISTOL MYERS SQUIBB CO
HWY 62 WEST BLDG 122
MOUNT VERNON, IN 47620
08-OCT-2002

FDA CDER EES

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

AADA:

Responsibilities: FINISHED DOSAGE PACKAGER

Profile: TCM

Last Milestone: OC RECOMMENDATION

Milestone Date: 26-NOV-01

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment:

DMP No:

Responsibilities:

Profile: TCM

Last Milestone: OC RECOMMENDATION

Milestone Date: 26-NOV-01

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

Establishment:

DMP No:

Responsibilities:

Profile: TCM

Last Milestone: OC RECOMMENDATION

Milestone Date: 26-NOV-01

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: CFNS: FEI

CITSUKA PHARMACEUTICAL CO LTD

MATSUTANI ITANO-CRO ITANO-GUN

TOKUSHIMA, JA

DMP No:

Responsibilities: FINISHED DOSAGE MANUFACTURER

FINISHED DOSAGE OTHER TESTER

FINISHED DOSAGE STABILITY TESTER

Profile: CTL

Last Milestone: OC RECOMMENDATION

Milestone Date: 19-JUL-02

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION
Chemistry Assessment Section

08-OCT-2002

FDA CDER RES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Profile: TCM
Last Milestone: OC RECOMMENDATION
Milestone Date: 19-JUL-02
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: CPN: 9611255
FEI: 3002807834
OTSUKA PHARMACEUTICAL CO LTD, SECOND TOKUSHIMA FACTORY
KAWAUCHI-CHO (2ND TOKUSHIMA), TOKUSHIMA, JA

Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE PACKAGER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER

Profile: CSN
Last Milestone: OC RECOMMENDATION
Milestone Date: 09-JUL-02
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment:

DMF No:

Responsibilities:

Profile: TCM
Last Milestone: OC RECOMMENDATION
Milestone Date: 26-NOV-01
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

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/s/

Sherita McLamore  
10/22/02 12:51:51 PM  
CHEMIST

Thomas Oliver  
10/22/02 12:59:06 PM  
CHEMIST

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