CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-729

CHEMISTRY REVIEW(S)

NDA 21-729

Abilify® Discmelt™ (aripiprazole) Orally Disintegrating Tablets

Otsuka Pharmaceutical Co. Ltd

Gurpreet Gill-Sangha, Ph.D.
OFFICE OF NEW DRUG AND QUALITY ASSESSMENT (ONDQA)

Review of Chemistry, Manufacturing, and Controls

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List of Tables:

Chemistry Review Data Sheet

1. NDA 21-729

2. REVIEW #: 3

3. REVIEW DATE: June 7, 2006

4. REVIEWER: Gurpreet Gill-Sangha, Ph.D.

5. PREVIOUS DOCUMENTS: None

Previous Documents	Document Date
Original NDA submission	December 22. 2003
Amendment C	January 13, 2004
Amendment BC	March 31, 2004
Amendment BC	July 8, 2004
Amendment BC	August 4, 2004
Amendment BC	August 20, 2004
Chemistry review #1	October 15, 2004
Chemistry review #2	October 29, 2004
Approvable (AE) Letter	October 22, 2004

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment C	October 28, 2004
Amendment AZ	December 12, 2005
Amendment BZ	April 13, 2006
Amendment BL	May 12, 2006
Amendment (by email)	May 15, 2006
Amendment (by email)	June 1, 2006
Amendment (by email)	June 6, 2006

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., Senior Director, Regulatory Affairs/Abilify
Telephone:	(301) 990-0030

Chemistry Review Data Sheet

* It is noted that the following is the authorized US agent name and address:

Kusuma Mallikaarjun, Ph.D., Senior Director
Otsuka Maryland Research Institute, Inc.
2440 Research Boulevard
Rockville, MD 20850

* Cover letter states that Bristol-Myers Squibb (BMS) is delegated to act on behalf of Otsuka Pharmaceuticals Co. (OPC) for correspondence. The CMC contact is:

Mary Peters, Director, Global Regulatory Sciences – CMC @ (609) 818-5521

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: Abilify
   b) Non-Proprietary Name (USAN): Aripiprazole
   c) Code Name/# (ONDC only): None
   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: Orally Disintegrating Tablets

12. STRENGTH/POTENCY: 10, 15, 20, and 30 mg * (* will initially launch 10 and 15 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

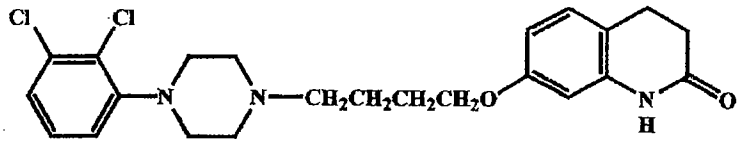
__X___Not a SPOTS product

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

CA Name: 7-[4-[4-(2,3-Dichlorophenyl)-1-piperazinyl] butoxy]-3,4-dihydrocarbostyril
USAN Name: Aripiprazole
Chemical Formula: $C_{23}H_{27}Cl_2N_3O_2$
Molecular Weight: 448.39

Chemistry Review Data Sheet

CAS registry #: 1279722-12-9
Laboratory Code: OPC-14597, OPC-31, BMS-337039-01
Structure:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs: None for this review

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS

[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: None for this review

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not Applicable		
EES	Acceptable	January 24, 2006	Shirnette Ferguson
Pharm/Tox	Acceptable	Refer to CMC review #1	Sonia Tabacova, Ph.D.
Biopharm	Acceptable	January 22, 2006, review #2	Kofi Kumi, Ph.D.

Chemistry Review Data Sheet

LNC	USAN Available	NA	
Methods Validation	Acceptable	As per CMC review #1	Gurpreet Gill-Sangha, Ph.D.
OPDRA (DMETS)	Acceptable	May 31, 2006, review #2	Denise Toyer, Pharm.D.
EA	Acceptable – categorical exclusion granted	As per CMC review #1	Gurpreet Gill-Sangha, Ph.D.
Microbiology	Not applicable		

The Chemistry Review for NDA 21-729

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 21-729 for Abilify® Discmelt™ (aripiprazole) Orally Disintegrating Tablets is recommended for APPROVAL from the CMC standpoint. Bristol Myers Squibb has addressed all the CMC issues as outlined in Chemistry Review's #1, #2 and #3 and in addition, FDA's Office of Compliance has issued an overall acceptable recommendation for all manufacturing and testing sites on January 24, 2006. A separate audit by FDA Compliance conducted on May 24 and 25, 2006 also found specific concerns with BMS site in Mayaguez acceptable (see Attachment 4).

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

None as per this review.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Abilify (aripiprazole) Orally disintegrating tablets (ODT) are indicated for the treatment of schizophrenia. Abilify ODT is a new aripiprazole dosage form especially for those patients who may have difficulty swallowing tablets. Currently, Abilify tablets in strengths of 2, 5, 10, 15, 20 and 30 mg approved (November 15, 2002) under NDA 21-436 are available. Abilify ODTs are to be marketed as 10, 15, 20, and 30 mg orally disintegrating tablets in unit blisters of 30 and 100 counts per pack. [redacted] BMS states that initially they propose to launch only the 10 and 15 mg strengths.

The drug substance aripiprazole is same as the one approved in NDA 21-436. It is noted that the original NDA 21-436 was not in the CTD-Q format as the current NDA and certain sections of drug substance are different in the CTD-Q format and therefore could not be reviewed as CTD-Q application. However, since the drug has been approved and marketed, the relevance of these sections is less of a concern. Aripiprazole is manufactured by Otsuka Pharmaceuticals, Japan and its specifications are the same as in the approved NDA 21-436. Certificate of analysis (CoAs) of five aripiprazole batches used to manufacture the Abilify ODT batches were provided. [redacted] date was granted to aripiprazole at 25 °C/60%RH as part of NDA 21-436.

Abilify ODT is formulated for oral administration in strengths of 10, 15, 20 and 30 mg. The tablets contain the active aripiprazole, calcium silicate [redacted] croscarmellose sodium and crospovidone [redacted] silicon dioxide [redacted] microcrystalline cellulose [redacted] magnesium stearate [redacted] xylitol, aspartame and acesulfame potassium [redacted] In addition, crème de vanilla is used as a flavor and tartaric acid [redacted] Red ferric oxide (pink) is used for 10 and 30 mg tablets and yellow ferric oxide (yellow) is used for 15 mg tablets. 20 mg tablets are white in color (no colorant added). Even though the 10 and 30 mg are identical in color (pink), they are distinguishable in size and debossings for individual strengths.

The ODTs are manufactured [redacted] followed by [redacted] form the tablets. In this resubmission, BMS has provided a well designed study to establish that aspartame does not interact with aripiprazole or other excipients in the ODT formulation. In addition, BMS has provided rationale and justification for use of croscarmellose sodium [redacted] in addition to crospovidone for the ODT formulation by demonstrating the dissolution profiles of the Abilify ODT containing croscarmellose sodium are similar to the Abilify tablets.

The commercial batch size is [redacted] tablets varying by the strength) and [redacted] batches were manufactured for this NDA as [redacted] batches of [redacted] 30 mg, [redacted] batches of 10 and 15 and [redacted] batch of 20 mg. All the batches were manufactured at Bristol Myers Squibb (BMS), Mayaguez, Puerto Rico. A [redacted] tablet press [redacted] was used for batches manufactured for this NDA and based on the information from FDA inspection during May 2004, batches were rejected due to [redacted] tablet problems. BMS proposed to change [redacted] ablet press [redacted] . BMS has provided data for 10, 15, 20 and 30 mg Abilify ODT tablets for Process Justification [redacted] validation [redacted]) and commercial [redacted] of 10- and 15- mg batches). It is noted that the rejection rate from Process Justification (PJ) and validation batches was still high at approximately up to [redacted] . Data requested during several teleconferences between BMS and Drs. Gurpreet Gill-Sangha and Thomas Oliver and the FDA audit conducted during May 24-25, 2006 revealed that the [redacted] tablet press was operated [redacted] for the Process Justification and validation batches due to software problems. However, the software has been validated for the commercial batches and the [redacted] is now under [redacted] resulting in small amounts of rejected materials [redacted] The sampling plan for the [redacted] tablet press is detailed in this review and it is acceptable to FDAs Office of Compliance also.

No specification for disintegration time was proposed in the original submission. BMS responded in mid-August 2004 to FDA's request in April 2004 for a disintegration specification. The responses were submitted on August 20, 2004 for all CMC issues (including those communicated in the 74-day letter). It is noted that BMS did not request a pre-NDA meeting with the chemistry team. Initially BMS proposed a

disintegration time of NMT [redacted] which was unacceptable and FDA requested BMS to propose a disintegration specification based on the recommendation of the Advisory Committee for Pharmaceutical Science meeting in October 21-22, 2003. In this resubmission, BMS has proposed a disintegration time of NMT 60 seconds which is acceptable as per the Advisory Committee recommendation. BMS has provided data from [redacted] batches which shows the disintegration time to be [redacted]. In addition, as per FDAs request BMS has updated the disintegration method to the USP disintegration method <701>. The specifications of identity by [redacted] were stated as "confirmed" which was unacceptable in the original submission. BMS has updated the identity test to include the [redacted] tests for routine testing. In addition, the dissolution specification of Q NLT [redacted] in 30 minutes was recommended as per review by Dr. Kofi Kumi during the original submission.

In the original submission, all the batches of Abilify ODT manufactured at BMS, Mayaguez, Puerto Rico were also packaged at the same site. However, the primary commercial packager for Abilify ODT is BMS, Mt. Vernon, Indiana and the secondary contract packagers are [redacted] The entire stability data collected including [redacted] at 25 °C/60%RH, [redacted]; at 40 °C/75%RH and 50 °C were from batches packaged at the BMS, Mayaguez, Puerto Rico site. No data were provided to show that the Abilify ODTs were acceptable prior to packaging at the commercial packaging sites and were able to withstand the transportation and bulk storage conditions. Due to nature of ODTs, possible softening and increased friability could occur. Therefore, BMS was requested to demonstrate that commercial Abilify ODTs (manufactured by BMS in Mayaguez, Puerto Rico, packaged in bulk containers, transported to a packaging site, and packaged in blisters) will remain within specifications at release and stability. BMS has provided a simulated shipping study in this resubmission to compare the pre- and post- shipping data which shows that results for moisture, hardness, and friability are similar. The disintegration time was below [redacted] with the BMS method instead of the proposed USP<701> for the commercial batches. Based on the stability data provided and the simulated study, an expiry of 24 months at 25 °C/60%RH is acceptable for Abilify ODT.

BMS has clarified in this resubmission that the specifications and test limits for post-approval stability are the same as stability and release except for not monitoring water, hardness and friability on post-approval. It should be noted that the commercial Abilify ODT will be blister packaged which do not experience the level of abrasion as the bottled tablets. An unknown impurity [redacted] was observed under accelerated conditions in the original submission. FDA had requested that this impurity should be identified and characterized as it is seen [redacted] BMS has provided acceptable rationale that the impurity was [redacted]

Information is provided for the labels of bulk containers, unit dose blisters and their cartons. The package insert also contains the precautionary statement for aspartame in the "Precautions" section as per 21 CFR 201.21(c) for amount of phenylalanine.

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

Aripiprazole orally disintegrating tablets will be supplied in four strengths: 10, 15, 20 and 30 mg. The orally disintegrating tablets will be packaged and marketed in unit dose aluminum/aluminum blisters. The trade packages for market launch will contain 30 and 100 tablets.

The recommended starting and target dose for Abilify ODT is 10 or 15 mg/day administered as a once-a-day schedule without regard to meals or liquid. The blister should not be opened until ready to administer. The tablet disintegration occurs in saliva.

An expiry of 24 months at 25 °C/60%RH is acceptable for Abilify ODT.

C. Basis for Approvability or Not-Approval Recommendation

NDA 21-729 for Abilify® Discmelt™ Orally Disintegrating Tablets is recommended for A**PPROVAL** based on the following:

- Adequate responses to CMC concerns related to the drug product sections as listed in Chemistry review #1 dated October 15, 2004 and included in the October 22, 2004 Approvable letter.
- Acceptable recommendation from FDA Compliance regarding cGMP status of manufacturing, packaging, controls and testing facilities dated January 24, 2006 and the Memo for FDA audit conducted on May 24 – 25, 2006.

III. Administrative

A. Reviewer's Signature

See electronic signature in Division File System (DFS).

B. Endorsement Block

See electronic signatures in DFS

C. CC Block

See DFS

51 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry-2

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

/s/

Gurpreet Gill-Sangha
6/7/2006 07:33:07 AM
CHEMIST

CMC review #3 for NDA 21-729

Thomas Oliver
6/7/2006 07:59:08 AM
CHEMIST

Initial Quality Assessment
Branch I

OND Division:	Division of Psychiatry Products
NDA:	**21-729**
Applicant:	Otsuka Pharmaceutical Co. Ltd
Letter Date:	12-DEC-05
Stamp Date:	13-DEC-05
PDUFA Date:	**13-JUN-06**
Trademark:	Abilify™ Orally Disintegrating Tablets
Established Name:	aripiprazole
Dosage Form:	Orally Disintegrating Tablets (10, 15, 20 and 30 mg)
Route of Administration:	Oral
Indication:	Schizophrenia
Assessed by:	**Thomas F. Oliver, Ph.D.**

Summary
Abilify® (aripiprazole) Orally Disintegrating Tablets were developed to treat schizophrenia, especially for those patients who have difficulty swallowing tablets. Aripiprazole was discovered by Otsuka Pharmaceutical co., Ltd. and co-developed with Bristol-Myers Squibb Company. The sponsor has two other approved aripiprazole products: 1) Abilify Tablets [AP, 15-NOV-02], and 2) Abilify Oral Solution [AP, 10-DEC-04]. The original NDA was submitted December 22, 2003. The sponsor was sent an AE letter dated October 22, 2004. The sponsor has responded to that letter in an electronic submission dated December 12, 2005.

Comments and Recommendation:
The sponsor has responded to each of the issues detailed in the October 22, 2004 AE letter. The sites have been resubmitted to the Office of Compliance and have been found acceptable as of January 24, 2006. As Dr. Gurpreet Gill-Sangha evaluated the original NDA, she would be a prudent choice as the CMC reviewer of this resubmission.

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

/s/

Thomas Oliver
2/1/2006 10:01:30 AM
CHEMIST

Ramesh Sood
2/2/2006 09:53:10 AM
CHEMIST

NDA 21-729

Abilify™ (aripiprazole) Orally Disintegrating Tablets

Otsuka Pharmaceutical Co. Ltd

Gurpreet Gill-Sangha, Ph.D.
DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-729

2. REVIEW #: 2

3. REVIEW DATE: October 28, 2004

4. REVIEWER: Gurpreet Gill-Sangha, Ph.D.

5. PREVIOUS DOCUMENTS: None

Previous Documents	Document Date
Original NDA submission	December 22. 2003
Amendment C	January 13, 2004
Amendment BC	March 31, 2004
Amendment BC	July 8, 2004
Amendment BC	August 4, 2004
Amendment BC	August 20, 2004

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original NDA submission	December 22. 2003

7. NAME & ADDRESS OF APPLICANT:

Name:	Otsuka Pharmaceutical Co., Ltd.
Address:	2-9 Kanda Tsukasa-cho Chiyoda-ku Tokyo, 101-8535, Japan
Representative:	Ms. Susan H. Behling, Director, Regulatory Science, Bristol-Myers Squibb Co.
Telephone:	(203) 677-3810

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: Abilify
   b) Non-Proprietary Name (USAN): Aripiprazole
   c) Code Name/# (ONDC only): None
   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: Orally Disintegrating Tablets

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

13. ROUTE OF ADMINISTRATION: Oral

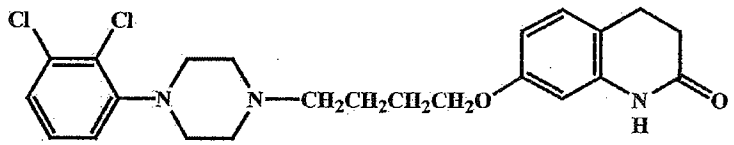
14. Rx/OTC DISPENSED: _X__Rx ___OTC

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:

CA Name: 7-[4-[4-(2,3-Dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydrocarbostyril
USAN Name: Aripiprazole
Chemical Formula: $C_{23}H_{27}Cl_2N_3O_2$
Molecular Weight: 448.39
CAS registry #: 1279722-12-9
Laboratory Code: OPC-14597, OPC-31, BMS-337039-01
Structure:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs: None for this review

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS

[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

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not Applicable		
EES	Withhold	October 22, 2004	Shirnette Ferguson
Pharm/Tox	Acceptable as per email dated 9/24/04 and review dated October 13, 2004	September 24, 2004 (email) and review October 13, 2004	Sonia Tabacova, Ph.D.
Biopharm	Acceptable	September 23, 2004	Kofi Kumi, Ph.D.
LNC	USAN Available	NA	
Methods Validation	Acceptable	As per this review	Gurpreet Gill-Sangha, Ph.D.
OPDRA (DMETS)	Acceptable	August 13, 2004	Kristina C. Arnwine, Pharm.D.
EA	Acceptable – categorical exclusion granted	As per this review	Gurpreet Gill-Sangha, Ph.D.
Microbiology	Not applicable		

The Chemistry Review for NDA 21-729

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 21-729 for Abilify™ (aripiprazole) Orally Disintegrating Tablets is recommended NOT APPROVABLE from the CMC standpoint. The FDA's Office of Compliance has issued a Withhold recommendation due to unresolved cGMP issues for the only drug product manufacturing site (CFN # 2627673) in Mayaguez, Puerto Rico. The approval is contingent on an overall acceptable recommendation from FDA Compliance and adequate responses to CMC deficiencies outlined in Chemistry review #1 dated October 15, 2004.

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

None as per this review.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Abilify (aripiprazole) Orally disintegrating tablets (ODT) are indicated for the treatment of schizophrenia. Abilify ODT is a new aripiprazole dosage form especially for those patients who may have difficulty swallowing tablets. Currently, Abilify tablets in strengths of 2, 5, 10, 15, 20 and 30 mg approved (November 15, 2002) under NDA 21-436 are available. Abilify ODTs are to be marketed as [redacted] 10, 15, 20, and 30 mg orally disintegrating tablets in unit blisters of 30 and 100 counts per pack.

The drug substance aripiprazole is same as the one approved in NDA 21-436. It is noted that the original NDA 21-436 was not in the CTD-Q format as the current NDA and certain sections of drug substance are different in the CTD-Q format. However, since the drug has been approved and marketed, the relevance of these sections is less of a concern. Aripiprazole is manufactured by Otsuka Pharmaceuticals, Japan and its specifications are the same as in the approved NDA 21-436. Certificate of analysis (CoAs) of five aripiprazole batches used to manufacture the Abilify ODT batches were provided. [redacted] date was granted to aripiprazole at 25 °C/60%RH as part of NDA 21-436.

Abilify ODT is formulated for oral administration in strengths of [redacted] 10, 15, 20 and 30 mg. The tablets contain the active aripiprazole, calcium silicate as

[redacted] croscarmellose sodium and crospovidone as [redacted] silicon dioxide as [redacted] t, microcrystalline cellulose [redacted] magnesium stearate as [redacted], xylitol, aspartame and acesulfame potassium as sweeteners. In addition, crème de vanilla is used as a flavor and tartaric acid is used as [redacted] FD&C Blue #2 Aluminum Lake (blue) is used as color for 5 mg tablets, red ferric oxide (pink) is used for 10 and 30 mg tablets and yellow ferric oxide (yellow) is used for 15 mg tablets. 20 mg tablets are white in color (no colorant added). Even though the 10 and 30 mg are identical in color (pink), they are distinguishable in size and debossings for individual strengths.

The ODTs are manufactured [redacted] followed by [redacted] form the tablets. No data was provided to show compatibility of excipient aspartame with the active or other excipients. In addition, no justification is provided in the pharmaceutical development section for use of croscarmellose sodium [redacted] in addition to crospovidone. The commercial batch size is [redacted] tablets varying by the strength) and [redacted] batches were manufactured for this NDA as [redacted] batches of [redacted] 30 mg, [redacted] batches of 10 and 15 and [redacted] batch of 20 mg. All the batches were manufactured at Bristol Myers Squibb (BMS), Mayaguez, Puerto Rico. A [redacted] tablet press was used for batches manufactured for this NDA and based on the information from FDA inspection, a significant number of batches were rejected due to [redacted] tablet problems. The sponsor proposes to change from a [redacted] tablet press post-approval for commercial batches without any validation to be provided to the Agency. Sponsor is requested to provide tablet data using the [redacted] tablet press with one batch of each strength of Abilify ODT to show validation of the [redacted] tablet press.

No specification for disintegration time was proposed in the original submission. BMS responded in mid-August 2004 to FDA's request in April 2004 for a disintegration specification. The responses were submitted on August 20, 2004 for all CMC issues (including those communicated in the 74-day letter). It is noted that BMS did not request a pre-NDA meeting with the chemistry team. BMS has provided data from [redacted] batches which shows the disintegration time to be [redacted] however, they have proposed a disintegration time of NMT [redacted] which is unacceptably long for an ODT and also the batch data for [redacted] batches shows the disintegration time to be [redacted] FDA will request BMS to propose a disintegration specification based on the recommendation of the Advisory Committee for Pharmaceutical Science meeting in October 21-22, 2003. The Advisory committee stated that a disintegration time of even 60 seconds was too long for an orally disintegrating tablet. In addition, BMS will be requested to update the disintegration method to mimic the criteria similar to the USP disintegration method <701>. The specifications of identity by [redacted] are currently stated as "confirmed" which is unacceptable. BMS will be requested to provide more precise specifications for identity by [redacted] and also include [redacted] as for routine release testing. In addition, the dissolution specification of Q NLT [redacted], in 30 minutes is

recommended as per review by Dr. Kofi Kumi. BMS is requested to provide the updated drug product specifications to reflect all the changes.

All the [redacted] batches of Abilify ODT manufactured at BMS, Mayaguez, Puerto Rico were also packaged at the same site. However, the primary commercial packager for Abilify ODT is BMS, Mt. Vernon, Indiana and the secondary contract packagers are [redacted] The entire stability data collected including [redacted] at 25 °C/60%RH, [redacted] at 40 °C/75%RH and 50 °C were from batches packaged at the BMS, Mayaguez, Puerto Rico site. No data were provided to show that the Abilify ODTs are acceptable prior to packaging at the commercial packaging sites and were able to withstand the transportation and bulk storage conditions. Due to nature of ODTs, possible softening and increased friability can occur as seen from the simulated bulk stability data. Therefore, the sponsor will need to demonstrate that commercial Abilify ODTs (manufactured by BMS in Mayaguez, Puerto Rico, packaged in bulk containers, transported to a packaging site, and packaged in blisters) will remain within specifications at release and stability. The sponsor has not provided the bulk packaging conditions and release data from the commercial packaging site in Indiana or contract packagers at [redacted] for batches manufactured at BMS, Mayaguez. The shipping and release data from the commercial packaging sites are required due to the friable nature of the ODTs.

In addition, the specifications for tests were not provided for the stability and post-approval stability protocols. The post-approval stability protocol should also include tests for water, hardness and friability due to the nature of the tablets. An unknown impurity [redacted] was observed under accelerated conditions. This impurity should be identified and characterized as it is seen [redacted]

No information is provided for the labels of bulk containers, unit dose blisters and their cartons. The package insert should also contain the precautionary statement for aspartame in the "Precautions" section as per 21 CFR 201.21(c) for amount of phenylalanine. BMS has also used the word [redacted] but not provided a justification for its use.

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

Aripiprazole orally disintegrating tablets will be supplied in [redacted] strengths: [redacted] 10, 15, 20 and 30 mg. The orally disintegrating tablets will be packaged and marketed in unit dose aluminum/aluminum blisters. The trade packages for market launch will contain 30 and 100 tablets.

The recommended starting and target dose for Abilify ODT is 10 or 15 mg/day administered as a once-a-day schedule without regard to meals or liquid. The blister

should not be opened until ready to administer. The tablet disintegration occurs in saliva.

Stability data provided was all supportive data and therefore an expiry date is yet to be determined.

C. Basis for Approvability or Not-Approval Recommendation

NDA 21-729 for Abilify Orally Disintegrating Tablets is recommended **NOT PPROVABLE** based on the following:

- Withhold recommendation from FDA Compliance regarding cGMP status of manufacturing, packaging, controls and testing facilities.
- Adequate responses to CMC concerns related to the drug product sections as listed in Chemistry review #1 dated October 15, 2004.

III. Administrative

A. Reviewer's Signature

See electronic signature in Division File System (DFS).

B. Endorsement Block

See electronic signatures in DFS

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/s/

Gurpreet Gill-Sangha
10/28/04 01:23:21 PM
CHEMIST

n21-729-cmc#2

Thomas Oliver
10/29/04 08:31:57 AM
CHEMIST

NDA 21-729

Abilify™ (aripiprazole) Orally Disintegrating Tablets

Otsuka Pharmaceutical Co. Ltd

Gurpreet Gill-Sangha, Ph.D.
DIVISION OF NEUROPHARMACOLOGICAL DRUG PRODUCTS

Review of Chemistry, Manufacturing, and Controls

Table of Contents

List of Tables:

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Chemistry Review Data Sheet

1. NDA 21-729

2. REVIEW #: 1

3. REVIEW DATE: October 14, 2004

4. REVIEWER: Gurpreet Gill-Sangha, Ph.D.

5. PREVIOUS DOCUMENTS: None

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original NDA submission	December 22. 2003
Amendment C	January 13, 2004
Amendment BC	March 31, 2004
Amendment BC	July 8, 2004
Amendment BC	August 4, 2004
Amendment BC	August 20, 2004

7. NAME & ADDRESS OF APPLICANT:

Name:	Otsuka Pharmaceutical Co., Ltd.
Address:	2-9 Kanda Tsukasa-cho Chiyoda-ku Tokyo, 101-8535, Japan
Representative:	Ms. Susan H. Behling, Director, Regulatory Science, Bristol-Myers Squibb Co.
Telephone:	(203) 677-3810

8. DRUG PRODUCT NAME/CODE/TYPE:
   a) Proprietary Name: Abilify
   b) Non-Proprietary Name (USAN): Aripiprazole
   c) Code Name/# (ONDC only): None
   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: Orally Disintegrating Tablets

12. STRENGTH/POTENCY: [redacted] 10, 15, 20, and 30 mg

13. ROUTE OF ADMINISTRATION: Oral

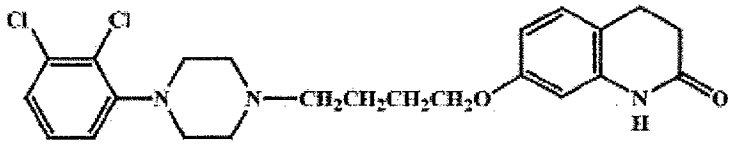
14. Rx/OTC DISPENSED: _X__Rx ___OTC

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:

CA Name: 7-[4-[4-(2,3-Dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydrocarbostyril
USAN Name: Aripiprazole
Chemical Formula: $C_{23}H_{27}Cl_2N_3O_2$
Molecular Weight: 448.39
CAS registry #: 1279722-12-9
Laboratory Code: OPC-14597, OPC-31, BMS-337039-01
Structure:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	IV	[redacted]		1	Adequate	September 2, 2004 by Gurpreet Gill-Sangha, Ph.D.	-

[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

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Pending		
EES	Pending		
Pharm/Tox	Acceptable as per email dated 9/24/04	September 24, 2004	Sonia Tabacova, Ph.D.
Biopharm	Acceptable	September 23, 2004	Kofi Kumi, Ph.D.
LNC	USAN Available	NA	
Methods Validation	Acceptable	As per this review	Gurpreet Gill-Sangha, Ph.D.
OPDRA	Pending		
EA	Acceptable – categorical exclusion granted	As per this review	Gurpreet Gill-Sangha, Ph.D.
Microbiology	Not applicable		

The Chemistry Review for NDA 21-729

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

NDA 21-729 for Abilify™ (aripiprazole) Orally Disintegrating Tablets is recommended APPROVABLE from the CMC standpoint. Currently, the San Juan, Puerto Rico District Office is recommending a withhold recommendation for the only drug product manufacturing site (CFN # 2627673) in Mayaguez, Puerto Rico. The approval is contingent on an overall acceptable recommendation from FDA Compliance and adequate responses to CMC deficiencies outlined in this review.

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

None as per this review.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Abilify (aripiprazole) Orally disintegrating tablets (ODT) are indicated for the treatment of schizophrenia. Abilify ODT is a new aripiprazole dosage form especially for those patients who may have difficulty swallowing tablets. Currently, Abilify tablets in strengths of 2, 5, 10, 15, 20 and 30 mg approved (November 15, 2002) under NDA 21-436 are available. Abilify ODTs are to be marketed as [redacted] 10, 15, 20, and 30 mg orally disintegrating tablets in unit blisters of 30 and 100 counts per pack.

The drug substance aripiprazole is same as the one approved in NDA 21-436. It is noted that the original NDA 21-436 was not in the CTD-Q format as the current NDA and certain sections of drug substance are different in the CTD-Q format. However, since the drug has been approved and marketed, the relevance of these sections is less of a concern. Aripiprazole is manufactured by Otsuka Pharmaceuticals, Japan and its specifications are the same as in the approved NDA 21-436. Certificate of analysis (CoAs) of five aripiprazole batches used to manufacture the Abilify ODT batches were provided. [redacted] date was granted to aripiprazole at 25 °C/60%RH as part of NDA 21-436.

Abilify ODT is formulated for oral administration in strengths of [redacted] 10, 15, 20 and 30 mg. The tablets contain the active aripiprazole, calcium silicate [redacted], croscarmellose sodium and crospovidone [redacted]

[redacted] silicon dioxide [redacted] microcrystalline cellulose [redacted] magnesium stearate [redacted] xylitol, aspartame and acesulfame potassium [redacted] In addition, crème de vanilla is used as a flavor and tartaric acid [redacted] FD&C Blue #2 Aluminum Lake (blue) is used as color for 5 mg tablets, red ferric oxide (pink) is used for 10 and 30 mg tablets and yellow ferric oxide (yellow) is used for 15 mg tablets. 20 mg tablets are white in color (no colorant added). Even though the 10 and 30 mg are identical in color (pink), they are distinguishable in size and debossings for individual strengths.

The ODTs are manufactured [redacted] followed by [redacted] form the tablets. No data was provided to show compatibility of excipient aspartame with the active or other excipients. In addition, no justification is provided in the pharmaceutical development section for use of croscarmellose sodium [redacted] in addition to crospovidone. The commercial batch size is [redacted] varying by the strength) and [redacted] batches were manufactured for this NDA as [redacted] batches of [redacted] 30 mg, [redacted] batches of 10 and 15 and [redacted] batch of 20 mg. All the batches were manufactured at Bristol Myers Squibb (BMS), Mayaguez, Puerto Rico. A [redacted] tablet press was used for batches manufactured for this NDA and based on the information from FDA inspection, a significant number of batches were rejected [redacted] tablet problems. The sponsor proposes to change [redacted] tablet press post-approval for commercial batches without any validation to be provided to the Agency. Sponsor is requested to provide tablet data using the [redacted] tablet press with one batch of each strength of Abilify ODT to show validation of the [redacted] tablet press.

No specification for disintegration time was proposed in the original submission. BMS responded in mid-August 2004 to FDA's request in April 2004 for a disintegration specification. The responses were submitted on August 20, 2004 for all CMC issues (including those communicated in the 74-day letter). It is noted that BMS did not request a pre-NDA meeting with the chemistry team. BMS has provided data from [redacted] batches which shows the disintegration time to be [redacted] however, they have proposed a disintegration time of NMT [redacted] which is unacceptably long for an ODT and also the batch data for [redacted] batches shows the disintegration time to be [redacted] FDA will request BMS to propose a disintegration specification based on the recommendation of the Advisory Committee for Pharmaceutical Science meeting in October 21-22, 2003. The Advisory committee stated that a disintegration time of even 60 seconds was too long for an orally disintegrating tablet. In addition, BMS will be requested to update the disintegration method to mimic the criteria similar to the USP disintegration method <701>. The specifications of identity by [redacted] are currently stated as "confirmed" which is unacceptable. BMS will be requested to provide more precise specifications for identity by [redacted] and also include [redacted] as for routine release testing. In addition, the dissolution specification of Q NLT [redacted] in 30 minutes is recommended as per review by Dr. Kofi Kumi. BMS is requested to provide the updated drug product specifications to reflect all the changes.

All the [redacted] batches of Abilify ODT manufactured at BMS, Mayaguez, Puerto Rico were also packaged at the same site. However, the primary commercial packager for Abilify ODT is BMS, Mt. Vernon, Indiana and the secondary contract packagers are [redacted] The entire stability data collected including [redacted] at 25 °C/60%RH, [redacted] at 40 °C/75%RH and 50 °C were from batches packaged at the BMS, Mayaguez, Puerto Rico site. No data were provided to show that the Abilify ODTs are acceptable prior to packaging at the commercial packaging sites and were able to withstand the transportation and bulk storage conditions. Due to nature of ODTs, possible softening and increased friability can occur as seen from the simulated bulk stability data. Therefore, the sponsor will need to demonstrate that commercial Abilify ODTs (manufactured by BMS in Mayaguez, Puerto Rico, packaged in bulk containers, transported to a packaging site, and packaged in blisters) will remain within specifications at release and stability. The sponsor has not provided the bulk packaging conditions and release data from the commercial packaging site in Indiana or contract packagers at [redacted] for batches manufactured at BMS, Mayaguez. The shipping and release data from the commercial packaging sites are required due to the friable nature of the ODTs.

In addition, the specifications for tests were not provided for the stability and post-approval stability protocols. The post-approval stability protocol should also include tests for water, hardness and friability due to the nature of the tablets. An unknown impurity at [redacted] was observed under accelerated conditions. This impurity should be identified and characterized as it is seen to grow under accelerated conditions during stability.

No information is provided for the labels of bulk containers, unit dose blisters and their cartons. The package insert should also contain the precautionary statement for aspartame in the "Precautions" section as per 21 CFR 201.21(c) for amount of phenylalanine. [redacted]

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

Aripiprazole orally disintegrating tablets will be supplied in [redacted] strengths: [redacted] 10, 15, 20 and 30 mg. The orally disintegrating tablets will be packaged and marketed in unit dose aluminum/aluminum blisters. The trade packages for market launch will contain 30 and 100 tablets.

The recommended starting and target dose for Abilify ODT is 10 or 15 mg/day administered as a once-a-day schedule without regard to meals or liquid. The blister should not be opened until ready to administer. The tablet disintegration occurs in saliva.

Stability data provided was all supportive data and therefore an expiry date is yet to be determined.

C. Basis for Approvability or Not-Approval Recommendation

NDA 21-729 for Abilify Orally Disintegrating Tablets is recommended **APPROVABLE** from the CMC standpoint based on the following:

- Pending overall recommendation from FDA Compliance regarding cGMP status of manufacturing, packaging, controls and testing facilities.
- Adequate responses to CMC concerns related to the drug product sections as listed on pages 102-103 of this review.

III. Administrative

A. Reviewer's Signature

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B. Endorsement Block

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C. CC Block

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/s/

Gurpreet Gill-Sangha
10/14/04 03:58:40 PM
CHEMIST

CMC review 1 for NDA 21-729

Thomas Oliver
10/15/04 07:45:37 AM
CHEMIST