

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number **21-436**

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

K1.1A



K1.1A

N21436



N21436

Aripiprazole
10mg, 15mg, 30mg
Tablets

REC.
12/6/02

Otsuka /BMS

NDA 21-436

Approvable
Package

Vol. 1

Antipsychotic

CAT: 1S

Goal Date
August 31, 2002 (10mos)

Greg Dubitsky (clinical)
Robert Harris (clinical)
Lois Freed (pharm/tox)
Gurpreet Gill-Sangha (chemistry)
Hong Zhao (biopharm)
Yeh-Fong Chen (stat)

NDA ACTION LETTER ROUTING RECORD

NDA#: 21-436

Date Received: August 16, 2002

Drug: aripiprazole

Division: HFD- 120

Type of Letter: AP AE NA

Drug Classification: 15

Patent Info Received: Yes (per PM) Safety Update: submitted but AE letter asks for updated update.

Phase IV Commitment: N/A

REVIEWER

RECEIPT

ACTION

1. Colleen LoCicero Date 8/24/02 Initials CU Date 8/24/02 Initials CU
Associate Director ① Where are carton + container labels located in action package? ② Please see for Regulatory Affairs suggested changes to the letter re - phase 4 commitments, Hadenema ③ MUA TL taken references 2 cop² mhp + 7/21/01 pre-NDA meeting. Minutes of these meetings not
Comments: User fee goal date - 8/31/02 reflected in checklist or included in package.
2. Chemistry Review Date 8.19.02 Initials JSS Date 8.20 Initials JSS
Comments: _____
3. Pharmacology & Toxicology Review Date _____ Initials _____ Date _____ Initials over
Comments: _____
3. R Behrman, M.D. Date _____ Initials _____ Date _____ Initials _____
Dep Director, ODEI
Comments: _____
4. R. Temple, M.D. Date 8/24/02 Initials RT Date 8/24/02 Initials RT
Director, Office of Drug Evaluation I
Returned to Division for Corrections _____ Forwarded _____
Letter Signed RT
Comments: _____

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NDA 21-436
Abilify (aripiprazole) Tablets

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 - Original Sponsor Labeling
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- I. Advisory Committee Meeting
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- K. Clinical Review
- L. Safety Update Review
- M. Pediatric Page
- N. Statistical Review
- O. Clinical Inspection Review Summary (DSI)
- P. Biopharmaceutical Review
- Q. CMC Review
- R. Nonclinical Pharmacology / Toxicology Information
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 - Statistical Review of Carcinogenicity Study
 - CAC/ECAC Report

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-436	Efficacy Supplement Type SE-	Supplement Number
Drug: Abilify (aripiprazole) Tablets		Applicant: Otsuka Pharmaceutical Co., Ltd.
RPM: Steven D. Hardeman, R.Ph.		HFD-120 Phone # 4-5525
Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)		Reference Listed Drug (NDA #, Drug name):
❖ Application Classifications:		
• Review priority		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
• Chem class (NDAs only)		1
• Other (e.g., orphan, OTC)		
❖ User Fee Goal Dates		August 31, 2002 (10 months)
❖ Special programs (indicate all that apply)		<input type="checkbox"/> None <input type="checkbox"/> Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review
❖ User Fee Information		
• User Fee		<input checked="" type="checkbox"/> Paid
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other
• User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input type="checkbox"/> Other
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Exception for review (Center Director's memo)		n/a
• OC clearance for approval		n/a
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.		<input checked="" type="checkbox"/> Verified
❖ Patent		
• Information: Verify that patent information was submitted		<input checked="" type="checkbox"/> Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted		21 CFR 314.50(i)(1)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).		<input type="checkbox"/> Verified

Exclusivity (approvals only)	
• Exclusivity summary	Completed
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!</i>	() Yes, Application # _____ (*) No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	n/a
General Information	
❖ Actions	
• Proposed action	() AP () TA (*) AE () NA
• Previous actions (specify type and date for each action taken)	none
• Status of advertising (approvals only)	() Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	() Yes (*) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(*) None () Press Release () Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	in package
• Most recent applicant-proposed labeling	n/a
• Original applicant-proposed labeling	in package
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings (indicate dates of reviews and meetings)	in package
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	in package
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	in package
• Reviews	see CMC, DMETS reviews
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	n/a
• Documentation of discussions and/or agreements relating to post-marketing commitments	n/a
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	in package
❖ Memoranda and Telecons	in package
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	n/a
• Pre-NDA meeting (indicate date)	cmc 6-22-01
• Pre-Approval Safety Conference (indicate date; approvals only)	n/a
• Other	n/a

Advisory Committee Meeting	
• Date of Meeting	n/a
• 48-hour alert	n/a
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	n/a
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	in package
Clinical Information	
❖ Clinical review(s) (indicate date for each review)	6-12-02
❖ Microbiology (efficacy) review(s) (indicate date for each review)	n/a
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	see clinical review
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	complete
❖ Demographic Worksheet (NME approvals only)	see clinical review
❖ Statistical review(s) (indicate date for each review)	7-16-02
❖ Biopharmaceutical review(s) (indicate date for each review)	complete
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	n/a
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	5-28-02
• Bioequivalence studies	n/a
CMC Information	
❖ CMC review(s) (indicate date for each review)	8-13-02
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	complete
• Review & FONSI (indicate date of review)	
• Review & Environmental Impact Statement (indicate date of each review)	
❖ Micro (validation of sterilization & product sterility) review(s) (indicate date for each review)	n/a
❖ Facilities inspection (provide EER report)	Date completed: (*) Acceptable - one pending () Withhold recommendation
❖ Methods validation	() Completed (*) Requested () Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	outside package
❖ Nonclinical inspection review summary	
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	in package
❖ CAC/ECAC report	in package

EXCLUSIVITY-SUMMARY for NDA # 21-436 SUPPL # _____

Trade Name Abilify Generic Name aripiprazole

Applicant Name Otsuka Pharmaceutical Co., Ltd. HFD- 120

Approval Date November 15, 2002

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

a) Is it an original NDA? YES/Yes/ NO /___/

b) Is it an effectiveness supplement? YES /___/ NO /___/

If yes, what type(SE1, SE2, etc.)? _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

YES /Yes/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES / Yes / NO / /

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

Five

e) Has pediatric exclusivity been granted for this Active Moiety?

YES / / NO / No /

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES / / NO / No /

If yes, NDA # Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES / / NO / No /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /No/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____

NDA # _____

NDA # _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____

NDA # _____

NDA # _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

- (b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

- (1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

- (b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/
Investigation #2 YES /___/ NO /___/
Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

- (c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # _____
Investigation #__, Study # _____
Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

- (a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
!
IND # _____ YES /___/ ! NO /___/ Explain: _____
!
!
!
!
!
Investigation #2 !
!
IND # _____ YES /___/ ! NO /___/ Explain: _____
!
!
!
!
!
!

- (b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
!
YES /___/ Explain _____ ! NO /___/ Explain _____
!
!
!
!
!
Investigation #2 !
!
YES /___/ Explain _____ ! NO /___/ Explain _____
!
!
!
!
!
!

- (c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

Steven D. Hardeman, R.Ph.

Signature of Preparer
Title: Senior Regulatory Project Manager

CC:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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

/s/

Steve Hardeman
11/19/02 02:31:49 PM

Russell Katz
11/19/02 02:37:23 PM

**APPEARS THIS WAY
ON ORIGINAL**

CONSULTATION RESPONSE

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)**

DATE RECEIVED: 7/29/02

DUE DATE: 8/25/02

ODS CONSULT #: 00-0325-2

TO: Russell Katz, MD
Director, Division of Neuropharmacological Drug Products
HFD-120

THROUGH: Steven Hardeman, RPh
Project Manager
HFD-120

PRODUCT NAME:
Abilify
(Aripiprazole) Tablets, 10 mg, 15 mg,
and 30 mg
NDA#: 21-436

**NDA SPONSORS: Otsuka Pharmaceutical Inc. and
Bristol-Myers Squibb Co.**

SAFETY EVALUATOR: Charlie Hoppes, RPh, MPH

SUMMARY: In response to a consult from the Division of Neuropharmacological Drug Products (HFD-120), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name "Abilify™" to determine the potential for confusion with approved proprietary and established names as well as pending names.

DMETS RECOMMENDATION:

DMETS has no objections to the use of the proprietary name, Abilify. In addition, DMETS recommends implementation of the labeling revisions outlined in section III of this review to minimize potential errors with the use of this product. This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from the signature date of this document.

Carol Holquist, RPh
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-5161

Jerry Phillips, RPh
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

**Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; Rm. 15B32
Center for Drug Evaluation and Research**

PROPRIETARY NAME REVIEW

DATE OF REVIEW: August 9, 2002

NDA# 21-436

NAME OF DRUG: Abilify™ (Aripiprazole) Tablets, 10 mg, 15 mg, and 30 mg

NDA HOLDER: Otsuka Pharmaceutical Inc. and Bristol-Myers Squibb Co.

I. INTRODUCTION:

This consult is written in response to a request from the Division of Neuropharmacological Drug Products (HFD-120) for an assessment of the proposed proprietary name Abilify. The container labels and package insert labeling for Abilify were reviewed for possible interventions in minimizing medication errors. Additionally the sponsor submitted an independent analysis of the name for review and comment. This analysis was conducted by Med-E.R.R.S., a subsidiary of the Institute for Safe Medication Practices (ISMP).

Abilify is the third proposed proprietary name for this consult, DMETS previously reviewed the names, "Abilitat" and ———. Abilitat and ——— were not recommended by DMETS on October 3, 2001 and May 15, 2002 respectively.

PRODUCT INFORMATION

Abilify is the proposed proprietary name for aripiprazole, a quinolinone derivative. Its mode of action differs from typical and atypical antipsychotic drugs. Biochemically, aripiprazole has been shown to be a partial agonist at members of the D₂ family of dopamine receptors. Abilify is indicated for the treatment of schizophrenia. The recommended starting dose is 15 mg once daily administered without regard to meals. Abilify will be available as 10 mg, 15 mg, and 30 mg strengths in bottles of 30, 60, 90, and 500 tablet count as well as blister packs of 100 tablets.

II. RISK ASSESSMENT:

The medication-error staff of DMETS conducted a search of several standard published drug product reference texts^{1,2} as well as several FDA databases³ for existing drug names which sound-alike or

¹ MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).

² Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

look-alike to Abilify to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted⁴. The Saegis⁵ Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Abilify. Potential concerns regarding drug marketing and promotion related to the proposed names were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. The Expert Panel did not identify any proprietary or established name that was thought to have the potential for confusion with Abilify.
2. DDMAC did not have concerns with the name with regard to promotional claims.

B. PRESCRIPTION ANALYSIS STUDIES

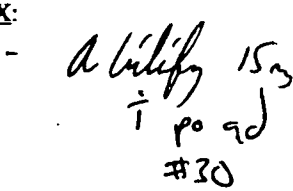
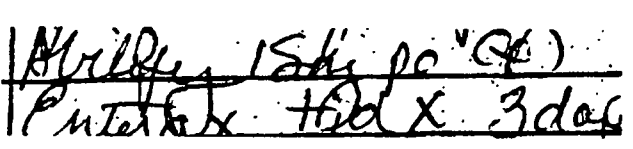
1. Methodology:

Three separate studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of Abilify with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 106 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescriptions for Abilify (see page 4). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

³ The Established Evaluation System [EES], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 00-02, and the electronic online version of the FDA Orange Book.

⁴ WWW location <http://www.uspto.gov/tmdb/index.html>.

⁵ Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com.

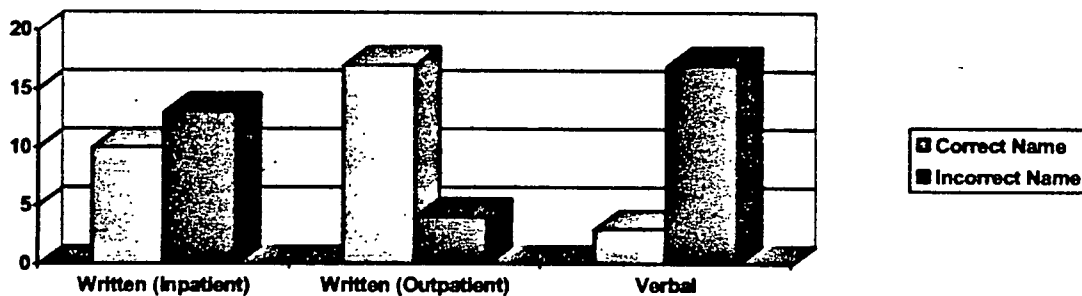
HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<u>Outpatient RX:</u> 	Abilify 15 mg 1 qd #30
<u>Inpatient RX:</u> 	

2. Results:

The results are summarized in Table I.

Table I

<u>Study</u>	<u># of Participants</u>	<u># of Responses (%)</u>	<u>Correctly Interpreted (%) "Abilify"</u>	<u>Incorrectly Interpreted (%)</u>
Written Inpatient	39	23 (59%)	10 (43%)	13 (57%)
Written Outpatient	35	21 (60%)	17 (81%)	4 (19%)
Verbal	32	20 (62%)	3 (15%)	17 (85%)
Total	106	64 (60%)	30 (47%)	34 (53%)



Among participants in the written prescription studies, 17 of 44 respondents (39%) interpreted the name incorrectly. The interpretations were misspelled variations of "Abilify". Incorrect interpretations of written prescriptions included: *Abilcy*, *Abildfy* (3 occurrences), *Abilily*, *Abilify*, *Albify*, *Abilefy* (2 occurrences), *Abilfy* (2 occurrences), *Ability*, *Abilixy*, *Atrilify* (2 occurrences), and *Abrilify* (2 occurrences).

Among participants in the verbal prescription studies, 17 of 20 (85%) interpreted the name incorrectly. Most incorrect name interpretations were phonetic variations of "Esilec". Incorrect interpretations of the verbal prescription included: *Adolofy*, *Abilafy*, *Abilafie* (2 occurrences), *Abiliphi*, *Abilophi*, *Adolaphi*, *Abilafy*, *Adelofi*, *Abilaffy*, *Abilifi* (2 occurrences), *Abilifide* (4 occurrences), and *Abilafi*.

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proposed proprietary name "Abilify", no products considered to have potential for name confusion with Abilify were identified in the U.S. marketplace. The prescription analysis studies did not yield any responses that might raise concern.

D. MED-E.R.R.S CONSULT

At the request of Bristol Myers Squibb Co., Med-E.R.R.S., a subsidiary of the Institute for Safe Medication Practices (ISMP), evaluated the trademark candidate Abilify to determine its potential for medication errors due to look-alike or sound-alike confusion with other medications. Practitioners identified as likely to use the product in their practice settings performed the Med-E.R.R.S. safety assessment for Abilify. Practitioners were asked to script Abilify, and respondents, which included pharmacists from both hospital and community pharmacy settings across the United States reviewed the handwritten samples of the trademark, and pronounced it according to pronunciation guidelines. The respondents took into consideration factors such as drug procurement, storage, dispensing, handling, administration, as well as the patient population. Data was assembled for analysis using a combination of Internet, email, and faxes.

No significant look-alike or sound-alike medications were identified by Med-E.R.R.S. as having possible look-alike or sound-alike similarities to Abilify.

Med-E.R.R.S. gave the name Abilify a rating of 5, the score indicating the lowest possible vulnerability for name confusion in the marketplace.

We agree with the conclusion provided by Med-E.R.R.S. that Abilify should not pose a significant safety risk.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

The name was found unacceptable in a DMETS consult dated May 15, 2002. As part of that consult, the following labeling and safety related issues were communicated to the Division. These comments should be forwarded to the sponsor if that has not yet been done.

In addition, DMETS has reviewed the blister label, container label, carton and insert labeling of and has identified several areas of possible improvement, which might minimize potential user error.

A. Blister Label

1. We note that the blister label is presented as a blister card while the carton labeling states that the "carton contains 10 strips with 10 tablets per strip". Please clarify whether a blister card or the strips will be utilized and revise accordingly.
2. The unit dose blister labels for the different strengths were not provided. We strongly recommend differentiating the product strength with the use of contrasting colors, boxing, or some other means.

B. Unit Dose Carton Labeling

1. See comment A1 and ~~A3~~ ^{*}A2. **per review 8/14/02*
2. A statement should be included as to whether or not the unit-dose package is child resistant. If not child resistant, we encourage the inclusion of a statement that if dispensed for outpatient use, it should be in a child resistant container. For example: This unit-dose package is not child resistant. If dispensed for outpatient use, a child resistant container should be utilized. (Note: The second sentence is optional.)

C. Container Label

1. See comment ~~A3~~ ^{*}A2.
2. We recommend relocating the net quantity statement "XX Tablets" so that it does not appear in close proximity to the strength of the product. Post-Marketing experience has demonstrated errors occurring as a result of the confusion with the net quantity and the strength.
3. The Poison Prevention Packaging Act notes that special packaging (child-resistant closure) should be the responsibility of the manufacturer when the container is clearly intended to be utilized in dispensing. Your proposed packages of 30s, 60s, and 90s appear to be in this category. Although the container label states that the medication should be dispensed in a tight container, it is not clear if the manufacturer provides the container with a child-resistant closure (CRC). If a CRC is not present, please revise accordingly.

D. Package Insert Labeling (DOSAGE AND ADMINISTRATION)

1. We recommend avoiding the use of abbreviation "QD", as abbreviations are prone to misinterpretation. We recommend that the abbreviation be written out as "once daily".

Although the recommended dose for is 15 mg once daily, the sponsor has stated that "the 10 mg strength would be available to allow physicians the discretion to provide a lower dose for patients on multiple concomitant inhibitors of CYP3A4 and 2D6 or who are particularly sensitive to antipsychotic medications." The current labeling does not contain this information for the 10 mg strength of . We recommend including this information to support the reasons for marketing the 10 mg strength.

V. RECOMMENDATIONS:

- A. DMETS has no objections to the use of the proprietary name Abilify.
- B. DMETS recommends the above labeling revisions that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from this date forward.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-3242.

Charlie Hoppes, RPh, MPH
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Alina Mahmud, RPh
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

**APPEARS THIS WAY
ON ORIGINAL**

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

/s/

Charles Hoppes
8/14/02 09:26:41 AM
PHARMACIST

Alina Mahmud
8/14/02 10:54:52 AM
PHARMACIST

Jerry Phillips
8/14/02 11:50:34 AM
DIRECTOR

APPEARS THIS WAY
ON ORIGINAL

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(ODS; HFD-400)**

ODS CONSULT #: 00-0325-1

THROUGH: Steven Hardeman
Project Manager
HFD-120

NDA#: 21-436

SAFETY EVALUATOR: Alina R. Mahmud, RPh.

In response to a consult from the Division of Neuropharmacological Drug Products (HFD-120), the Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name to determine the potential for confusion with approved proprietary and established names as well as pending names.

DMETS does not recommend the use of the proposed proprietary name _____. In addition, DMETS recommends implementation of the labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.

Jerry Phillips, RPh
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-400; Rm. 15B32
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: May 15, 2002

NDA 21-436

NAME OF DRUG: _____ (Aripipazole Tablets) 10 mg, 15 mg, 30 mg

NDA HOLDER: Otsuka Pharmaceutical Co., Ltd.

I. INTRODUCTION:

This consult is written in response to a request from the Division of Neuropharmacological Drug Products (HFD-120) for an assessment of the proposed proprietary name _____. The container label, carton and package insert labeling were reviewed for possible interventions in minimizing medication errors.

PRODUCT INFORMATION

_____ is the proposed proprietary name for aripiprazole, a quinolinone derivative. Its mode of action differs from typical and atypical antipsychotic drugs. Biochemically, aripiprazole has been shown to be a partial agonist at members of the D₂ family of dopamine receptors. _____ is indicated for the treatment of schizophrenia. The recommended starting dose is 15 mg once daily administered without regard to meals. _____ will be available as 10 mg, 15 mg, and 30 mg strengths in bottles of 30, 60, 90, 250, and 500 tablet count as well as blister packs of 100 tablets.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{1,2} as well as several FDA databases³ for existing drug names which sound alike or look alike to _____ to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted⁴. The Saegis⁵ Pharma-In-Use

¹ MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).

² Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

³ The Established Evaluation System [EES], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-00, and the electronic online version of the FDA Orange Book.

⁴ WWW location <http://www.uspto.gov/tmdb/index.html>.

⁵ Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com.

database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name . Potential concerns regarding drug marketing and promotion related to the proposed names were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. The Expert Panel identified one proprietary name that was thought to have the potential for confusion with . This product is listed in Table 1 (below), along with the dosage forms available and usual dosage.
2. DDMAC did not have concerns the name with regard to promotional claims.

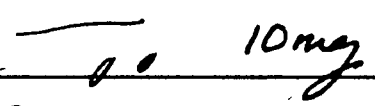
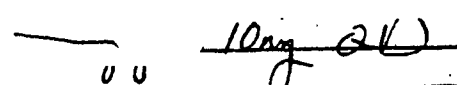
Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
<u> </u>	Aripiprazole Tablets 10 mg, 15 mg, 30 mg	15 mg once daily.	
Glipizide	Glipizide Tablets 5 mg and 10 mg	15 mg to 30 mg given once or twice daily	L/A
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)			

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of _____ with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 107 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for _____ (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

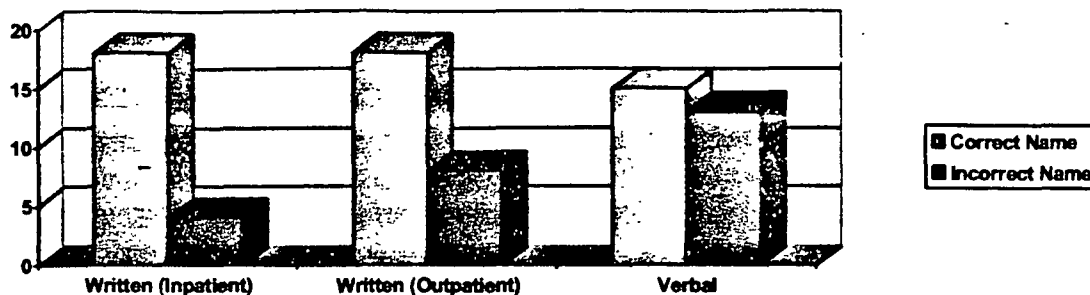
HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
	_____ 10 mg, Take 1 tablet once daily, #30
	

2. Results:

The results are summarized in Table I.

Table I

<u>Study</u>	<u># of Participants</u>	<u># of Responses (%)</u>	<u>Correctly Interpreted</u>	<u>Incorrectly Interpreted</u>
Written Inpatient	36	22 (61%)	18 (82%)	4 (18%)
Written Outpatient	33	26 (79%)	18 (69%)	8 (31%)
Verbal	38	28 (74%)	15 (54%)	13 (56%)
Total	107	76 (71%)	51 (67%)	25 (33%)



Among participants in the written prescription studies, 12 of 48 respondents (25%) interpreted the name incorrectly. The interpretations were misspelled variations of " ———". Incorrect interpretations of written prescriptions included: *Abligize* (6), *Aldigize*, *Abuligize*, and *Abiligize* (4).

Among participants in the verbal prescription studies, 13 of 28 (46%) interpreted the name incorrectly. Most incorrect name interpretations were phonetic variations of " ———". Incorrect interpretations of the verbal prescription included: *Aciligize*, *Abilogize* (3), *Abologizer*, *Abilagise*, *Abiligide*, *Abiligise*, *Avilagize*, and *Abilagize*.

C. SAFETY EVALUATOR RISK ASSESSMENT

The product considered having the greatest potential for name confusion with " ———" was Glipizide.

DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that " ———" can be confused with Glipizide. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to small sample size. The majority of interpretations from the written and verbal prescription studies were phonetic/misspelled interpretations of the drug name " ———".

Glipizide is an oral blood-glucose lowering drug of the sulfonylurea class. Glipizide is indicated as an adjunct to diet for the control of hyperglycemia and its associated symptomatology in patients with non-insulin-dependent diabetes mellitus (NIDDM; type II). The recommended starting dose is 5 mg at breakfast. The *maximum recommended once daily* dose is 15 mg per day. Doses greater than 15 mg per day should be divided in two doses. Although Glipizide and " ———" do not sound similar, the drug names can look similar when scripted (see writing sample on page 6). Both names share the letters "i" (times three) and "z", end with the letter "e", and contain letters that can look similar when scripted ("G" vs. "A", "b" vs. "l", and "p" vs. "g"). Post-Marketing experience has shown reports of confusion between drug names that share similar letters such as "Cozaar" and "Zocor". For example, one report indicated that a nurse rewrote a legibly written order for Cozaar as Zocor. In addition, each name consists of nine letters.

Furthermore, Glipizide and " ———" share an overlapping strength (10 mg), dosing regimen (once daily), and dosage form (tablets) and each can be prescribed in identical quantities (30 tablets). Moreover, Glipizide and " ———" can be dosed as 15 mg once daily. The inadvertent administration of Glipizide in place of " ———" can result in life-threatening consequences, such as hypoglycemia, coma, seizure, and other neurological impairment. The

inadvertent administration of _____ for Glipizide can result in hyperglycemia (untreated diabetes), tardive dyskinesia, orthostatic hypotension, and seizure. Neuroleptic Malignant Syndrome (NMS), a potential fatal symptom complex, has been reported in association with administration of antipsychotic drugs including _____

_____, 10 mg, Glipizide 10 mg
#30 #30
T O D T O D

Although the recommended dose for _____ is 15 mg once daily, the sponsor has stated that "the 10 mg strength would be available to allow physicians the discretion to provide a lower dose for patients on multiple concomitant inhibitors of CYP3A4 and 2D6 or who are particularly sensitive to antipsychotic medications." Therefore, it is possible that a prescription may be written for "_____ 10 mg". However, the current labeling does not contain this information for the 10 mg strength of _____. We recommend including this information to support the reasons for marketing the 10 mg strength.

III. COMMENTS TO THE SPONSOR

DMETS does not recommend the use of the proposed proprietary name _____

The product considered having the greatest potential for name confusion with _____ was Glipizide.

Glipizide is an oral blood-glucose lowering drug of the sulfonylurea class. Glipizide is indicated as an adjunct to diet for the control of hyperglycemia and its associated symptomatology in patients with non-insulin-dependent diabetes mellitus (NIDDM; type II). The recommended starting dose is 5 mg at breakfast. The recommended maintenance dose is 15 mg per day, given once daily or divided in two doses. Although Glipizide and _____ do not sound similar, the drug names can look similar when scripted (see writing sample below). Both names share the letters "i" (times three) and "z", end with the letter "e", and contain letters that can look similar when scripted ("G" vs. "A", "b" vs. "l", and "p" vs. "g"). In addition, each name consists of nine letters. Furthermore, Glipizide and _____ share an overlapping strength (10 mg), dosing regimen (once daily), and dosage form (tablets). Moreover, they can be prescribed in identical quantities (30 tablets). The inadvertent administration of Glipizide for _____ can result in life-threatening consequences, such as hypoglycemia, coma, seizure, and other neurological impairment. The inadvertent administration of _____ for Glipizide can result in hyperglycemia (untreated diabetes), tardive dyskinesia, orthostatic hypotension, and seizure. Neuroleptic Malignant Syndrome (NMS), a potential fatal symptom complex, has been reported in association with administration of antipsychotic drugs including _____

_____, 10 mg, Glipizide 10 mg
#30 #30
T O D T O D

Although the recommended dose for _____ is 15 mg once daily, the sponsor has stated that "the 10 mg strength would be available to allow physicians the discretion to provide a lower dose for patients on multiple concomitant inhibitors of CYP3A4 and 2D6 or who are particularly sensitive to antipsychotic medications." Therefore, it is possible that a prescription may be written for "_____ 10 mg". However, the current labeling does not contain this information for the 10 mg strength of _____. We recommend including this information to support the reasons for marketing the 10 mg strength.

In addition, DMETS has reviewed the blister label, container label, carton and insert labeling of _____ and has identified several areas of possible improvement, which might minimize potential user error.

A. Blister Label

1. We note that the blister label is presented as a blister card while the carton labeling states that the "carton contains 10 strips with 10 tablets per strip". Please clarify whether a blister card or the strips will be utilized and revise accordingly.
2. The labels provided suggest the product will be packaged as a blister card. At a minimum your blister label must bear the information outlined in 21 CFR 201.10(i). The proposed packaging could fall short of this requirement if the tablets are divided or pushed through the label. Revise label to include the proprietary and established name, strength, lot number, and expiration date over each tablet.
3. The unit dose blister labels for the different strengths were not provided. We strongly recommend differentiating the product strength with the use of contrasting colors, boxing, or some other means.

B. Unit Dose Carton Labeling

1. See comment A1 and A3.
2. A statement should be included as to whether or not the unit-dose package is child resistant. If not child resistant, we encourage the inclusion of a statement that if dispensed for outpatient use, it should be in a child resistant container. For example: This unit-dose package is not child resistant. If dispensed for outpatient use, a child resistant container should be utilized. (Note: The second sentence is optional.)

C. Container Label

1. See comment A3.
2. We recommend relocating the net quantity statement "XX Tablets" so that it does not appear in close proximity to the strength of the product. Post-Marketing experience has demonstrated errors occurring as a result of the confusion with the net quantity and the strength.
3. The Poison Prevention Packaging Act notes that special packaging (child-resistant closure) should be the responsibility of the manufacturer when the container is clearly intended to be utilized in dispensing. Your proposed packages of 30s, 60s, and 90s appear to be in this category. Although the container label states that the medication should be dispensed in a tight container, it is not clear if the manufacturer provides the container with a child-resistant closure (CRC). If a CRC is not present, please revise accordingly.

D. Package Insert Labeling (DOSAGE AND ADMINISTRATION)

1. We recommend avoiding the use of abbreviation "QD", as abbreviations are prone to misinterpretation. We recommend that the abbreviation be written out as "once daily".
2. Although the recommended dose for _____ is 15 mg once daily, the sponsor has stated that "the 10 mg strength would be available to allow physicians the discretion to provide a lower dose for patients on multiple concomitant inhibitors of CYP3A4 and 2D6 or who are particularly sensitive to antipsychotic medications." The current labeling does not contain this information for the 10 mg strength of _____. We recommend including this information to support the reasons for marketing the 10 mg strength.

IV. RECOMMENDATIONS:

- A. DMETS does not recommend the use of the proprietary name _____
- B. DMETS recommends the labeling revisions as outlined in Section III of this review that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-3242.

Alina Mahmud, RPh
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

APPEARS THIS WAY
ON ORIGINAL

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/s/

Alina Mahmud
6/4/02 11:32:30 AM
PHARMACIST

Carol Holquist
6/5/02 03:43:16 PM
PHARMACIST

Jerry Phillips
6/6/02 08:33:05 AM
DIRECTOR

**APPEARS THIS WAY
ON ORIGINAL**

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: October 2, 2000	DUE DATE: October 9, 2001	OPDRA CONSULT #: 00-0325
TO: Russell Katz, MD Director, Division of Neuropharmacological Drug Products HFD-120		
THROUGH: Steven Hardeman, Project Manager HFD-120		
PRODUCT NAME: Abilitat (aripiprazole) 15 mg and 30 mg	MANUFACTURER: Otsuka and Bristol Myers Squibb	
IND #: _____		
SAFETY EVALUATOR: Alina R. Mahmud, RPh.		
SUMMARY: In response to a consult from the Division of Neuropharmacological Drug Products (HFD-120), OPDRA conducted a review of the proposed proprietary name "Abilitat" to determine the potential for confusion with approved proprietary and generic names as well as pending names.		
PDRA RECOMMENDATION: OPDRA does not recommend the use of the proprietary name "Abilitat"		
<hr/> Jerry Phillips, R.Ph. Associate Director for Medication Error Prevention Office of Post-Marketing Drug Risk Assessment Phone: (301) 827-3246 Fax: (301) 480-8173		<hr/> Martin Himmel, M.D. Deputy Director Office of Post-Marketing Drug Risk Assessment Center for Drug Evaluation and Research Food and Drug Administration

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm. 15B32
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: October 3, 2001

IND NUMBER: _____

NAME OF DRUG: Abilitat
 (aripiprazole) 15 mg and 30 mg

IND HOLDER: Otsuka and Bristol Myers Squibb

I. INTRODUCTION

This consult was written in response to a request from the Division Neuropharmacological Drug Products (HFD-120), for assessment of the proprietary name "Abilitat", regarding potential name confusion with other proprietary/generic drug names.

PRODUCT INFORMATION

Abilitat is the proposed proprietary name for aripiprazole, a quinolinone derivative. Its mode of action differs from typical and atypical antipsychotic drugs. Biochemically, aripiprazole has been shown to be a partial agonist at members of the D₂ family of dopamine receptors. Abilitat is being evaluated in patients with acute schizophrenia, acute mania, psychosis associated with Alzheimer's dementia and treatment resistant schizophrenia. While starting doses for these various patient populations have not yet been determined, oral daily doses of 5- to 50 mg are under evaluation. The dosage form that will be submitted in the initial NDA is oral tablets. Although the NDA will definitely contain 15 mg and 30 mg strength tablets, the need for additional strengths is currently under discussion.

II. RISK ASSESSMENT

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts^{1,2,3} as well as several FDA databases⁴ for existing drug names which sound-alike or look-alike to "Abilitat" to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online

¹ MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Co. Inc, 2000).

² American Drug index, 42nd Edition, 1999, Facts and Comparisons, St. Louis, MO.

³ Facts and Comparisons, 2000, Facts and Comparisons, St. Louis, MO.

⁴ COMIS, The Established Evaluation System [EES], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, New Drug Approvals 98-00, and online version of the FDA Orange Book.

version of the U.S. Patent and Trademark Office's Text and Image Database and Thomson and Thomson was also conducted^{5,6}. An Expert Panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted three prescription analysis studies, to simulate the prescription ordering process.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by OPDRA to gather professional opinions on the safety of the proprietary name "Abilitat". Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of OPDRA Medication Errors Prevention Staff and representation from the Division of Drug Marketing and Advertising Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

Three product names were identified in the Expert Panel Discussion that were thought to have potential for confusion with "Abilitat". These products are listed in Table 1, along with the dosage forms available and usual FDA-approved dosage.

DDMAC did not have any concerns with the name in regard to promotional claims.

TABLE 1

Product Name	Dosage form(s), Generic name	Usual adult dose*	Other**
Abilitat	Aripiprazole tablets (Rx)	Oral daily doses of 5 to 30 mg	
Abelcet	Amphotericin B suspension for injection 100 mg/20 mL (Rx)	Individualized dosage based on patient's clinical status	S/A, L/A per OPDRA
Adalat	Nifedipine 10 mg, 20 mg CC (extended-release): 30 mg, 60 mg, and 90 mg (Rx)	Immediate release: 10mg to 20mg three times daily CC: 30 mg to 60 mg once daily	S/A, L/A per OPDRA
Habitrol	Nicotine transdermal system 7mg, 14 mg, and 21 mg (otc)	Apply one patch daily	S/A, L/A per OPDRA
		*Frequently used, not all-inclusive.	**L/A (look-alike), S/A (sound-alike)

B. STUDY CONDUCTED BY OPDRA

1. Methodology

A separate study was conducted within FDA for the proposed proprietary name to determine the degree of confusion of "Abilitat" with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 86 health care professionals (nurses, pharmacists, and physicians). This exercise was conducted in an attempt to simulate the prescription ordering process. An

⁵ WWW location <http://www.uspto.gov/tmdb/index.html>.

⁶ Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www.thomson-thomson.com.

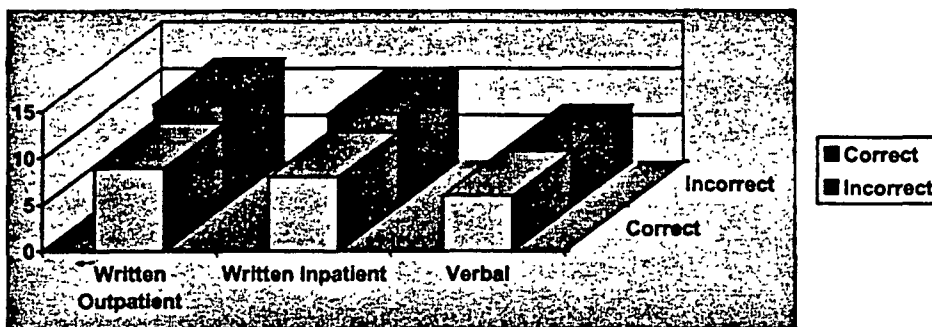
OPDRA staff member wrote an inpatient order and outpatient prescriptions, each consisting of a combination of marketed and unapproved drug products and prescriptions for "Abilitat" (see below). These written prescriptions were optically scanned and one prescription was delivered via email to each study participant. In addition, one OPDRA staff member recorded a verbal outpatient prescription that was then delivered to a group of study participants via telephone voicemail. Each reviewer was then requested to provide an interpretation of the prescription via email.

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTION
Outpatient: Abilitat 15 mg # 30 Sig: 1 po daily	Abilitat 15 mg Take 1 tablet once daily Dispense # 30
Inpatient: Abilitat 15 mg po daily	

2. Results

Results of these exercises are summarized below:

Study	No. of participants	# of responses (%)	"Abilitat" response	Other response
Written: Outpatient	28	20 (71%)	9 (45%)	11 (55%)
Written: Inpatient	28	18 (64%)	8 (44%)	10 (56%)
Verbal	30	12 (40%)	6 (50%)	6 (50%)
Total:	86	50 (58%)	23 (46%)	27 (54%)



Among participants in the two written prescription studies, 21 of 56 respondents (38%) interpreted the name incorrectly. The interpretations were misspelled variations of "Abilitat" such as *Habitat*, *Abelelat*, *Abelitat*, *Abiletat*, and *Abilitot*. Other participants provided *Hoilitat*, *Abilitol*, *Hailitat*, *Abelistat*, and *Hoilitot*. One participant interpreted the name as *Habitrol*, which is an approved drug product. *Adderal*, *Abelcet* and *Adalat* were also cited as having look-alike and/or sound-alike potential with *Abilitat*.

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name "Abilitat", the primary concern raised was related to a sound-alike, look-alike name that already exists in the U.S. marketplace. One product, Adalat, was believed to be the most problematic in terms of potential medication errors.

OPDRA conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that Abilitat could be confused with Adalat. However, one study participant noted Adalat as having look-alike and sound-alike potential with Abilitat. Adderal, Abelcet and Habitrol were also cited as having look-alike and sound-alike potential with Abilitat. However, these drug products and Abilitat lack convincing look-alike and sound-alike potential and differ in regards to dosage form, dosing regimen, route of administration, and strength. The majority of the participants from the verbal and two written prescription studies provided phonetic/misspelled interpretations to the proposed drug name.

Adalat is the proprietary name for nifedipine which is indicated for the management of Chronic Stable Angina and Vasospastic Angina. Adalat is available as an immediate release soft gelatin capsule containing 10mg and 20 mg of nifedipine. Adalat CC, an extended-release formulation of nifedipine, is available in 30 mg, 60 mg and 90 mg tablet strengths. Abilitat and Adalat not only look similar when scripted (see writing sample), the drug names sound similar as well. A prescription for Abilitat 30 mg has the potential to look and sound similar to Adalat 30 mg, which then may be misinterpreted as Adalat CC 30 mg (without further clarification from the prescriber) since Abilitat and Adalat (immediate release formulation) do not share an overlapping strength. The fact that Abilitat and Adalat CC share an overlapping dosage form and dosing schedule can add to the confusion. Additionally, the sponsor has notified the division that the need for additional tablet strengths for special populations or sensitive patients is currently under discussion. Therefore, the possibility of Abilitat and Adalat (or Adalat CC) having a greater number of overlapping strengths does exist. If a patient inadvertently receives Adalat instead of Abilitat, the patient may experience hypotensive episodes. A patient that inadvertently receives Abilitat instead of Adalat may experience side effects related Abilitat (package insert not available at this time).

Abilitat Adalat

III. RECOMMENDATION:

OPDRA does not recommend the use of the proprietary name "Abilitat".

OPDRA would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam, R.Ph. at 301-827-3231.

Alina R. Mahmud, R.Ph.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment (OPDRA)

Concur:

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment (OPDRA)

**APPEARS THIS WAY
ON ORIGINAL**

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

/s/

Alina Mahmud
10/9/01 10:17:31 AM
PHARMACIST

Jerry Phillips
10/10/01 10:32:08 AM
DIRECTOR

Martin Himmel
10/11/01 03:10:33 PM
MEDICAL OFFICER

**APPEARS THIS WAY
ON ORIGINAL**

Number of Pages
Redacted 54

25
27
+ 2



Draft Labeling
(not releasable,

— other drugs (not this NDA)

Aripiprazole
OPC-14597, BMS-337039

FDA Response

AGENCY COMMENT

Post Approval (Phase 4) Commitments

1. *Due to the limited solubility of aripiprazole and non-rapid dissolving nature of the tablet in gastric pH (pH 1.2), we ask that you commit to conducting a food effect study on the highest strength (30 mg).*
2. *In each of the 3 positive fixed dose studies, the lowest dose (10, 15, or 20 mg) was numerically superior to all the higher doses. You have thus not adequately explored the lower end of the dose response curve for effectiveness. We ask that you commit to conducting, postapproval, additional studies to determine whether or not doses lower than 10 mg are effective.*
3. *To address the longer-term efficacy of aripiprazole in the treatment of adults with schizophrenia, we request that you submit, post-approval, the results of Study 138047.*
4. *We ask that you commit to conducting, postapproval, additional studies in order to further characterize (e.g., reversibility, functional correlates) and, if possible, to determine the mechanism(s) underlying the retinal degeneration observed in the 26-wk and 2-yr carcinogenicity studies in Sprague-Dawley rat.*
5. *The data from studies conducted in rhesus monkey suggest that aripiprazole may have some abuse liability. One of 4 monkeys trained to self-administer cocaine continued to self-administer when aripiprazole was substituted for cocaine. In addition, 4 of 4 monkeys exhibited withdrawal symptoms following abrupt cessation of dosing with aripiprazole. Although self-stimulation was not observed in rats when aripiprazole was substituted for cocaine, there was a tendency for animals to exhibit withdrawal symptoms following abrupt cessation of dosing. Therefore, we ask that you commit to conducting, postapproval, additional studies investigating the abuse liability of aripiprazole.*

RESPONSE

We acknowledge the post approval (Phase 4) commitments listed above. We agree to these commitments and will be in contact with the Division shortly after approval regarding the submission of the requested data and, if necessary, to consult with the Division on the design of additional studies..



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-436

Otsuka Maryland Research Institute
Attention: Gary Ingenito, M.D., Ph.D.
President and Chief Operating Officer
2440 Research Boulevard
Rockville, MD 20850

Dear Dr. Ingenito:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: aripiprazole tablets
Review Priority Classification: Standard (S)
Date of Application: October 31, 2001
Date of Receipt: October 31, 2001
Our Reference Number: NDA 21-436

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on December 30, 2001 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be August 31, 2002 and the secondary user fee goal date will be October 31, 2002.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You

should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Under 21 CFR 314.102(c) of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug
Products, HFD-120
Attention: Division Document Room 4008
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neuropharmacological Drug
Products, HFD-120
Attention: Division Document Room 4008
1451 Rockville Pike
Rockville, Maryland 20852-1420

If you have any questions, call Steven D. Hardeman, R.Ph., Senior Regulatory Project Manager, at (301) 594-5525.

Sincerely,

{See appended electronic signature page}

John S. Purvis
Chief, Project Management Staff
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Steve Hardeman
11/6/01 09:25:33 AM
Signed for John Purvis.

**APPEARS THIS WAY
ON ORIGINAL**



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Otsuka Pharmaceutical Company, Ltd.
Attention: Kusuma Mallikaarjun, Ph.D.
Associate Director, Regulatory Affairs
2440 Research Boulevard
Rockville, MD 20850

Dear Dr. Mallikaarjun:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for aripiprazole.

We also refer to your amendment of August 23, 2000 (serial # 289), containing a request for review of the proposed proprietary name "Abilitat."

The Office of Post-Marketing Drug Risk Assessment has completed the proprietary name review of your submission and has determined that "Abilitat" is not in compliance with 21 CFR 201.10(c)(5). This regulation prohibits the designation of a drug or ingredient by a proprietary name that, because of similarity in spelling or pronunciation, may be confused with the proprietary name or the established name of a different drug or ingredient. In particular, the product "Adalat" was determined to be the most problematic in terms of potential medication errors. The products, "Abelcet" and "Habitrol" were also identified as having the potential for confusion with "Abilitat."

We request that you amend your application with an alternative proprietary name and following review by the Office of Post-Marketing Drug Risk Assessment, we will forward their recommendation.

If you have any questions, call Steven D. Hardeman, R.Ph., Senior Regulatory Project Manager, at (301) 594-5525.

Sincerely,

{See appended electronic signature page}

Russell Katz, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

MINUTES OF A MEETING

Meeting Date: February 19, 1997

FDA Participants: Dr. Paul Leber, Director, Division of Neuropharmacology
Dr. Tom Laughren, Psychopharmacology Team Leader
Dr. David Hoberman, Biometrics
Dr. Greg Dubitsky, Medical Reviewer
Dr. Lois Freed, Pharmacology Reviewer
Dr. Glenna Fitzgerald, Pharmacology Team Leader
Dr. Greg Burkhart, Medical Reviewer
Dr. Mohammad Hossain, Biopharmaceutics Team Leader
Steve Hardeman, R.Ph., Project Manager

Otsuka Participants: Dr. Jonathan Petrie, Clinical Project Director
Dr. Anutosh Saha, Clinical Scientist
Dr. Norma Browder, Non-clinical
Dr. Paul Chow, Non-clinical
Dr. Steve Bramer, Clinical Pharmacokinetics
Dr. Suresh Mallikaarjun, Clinical Pharmacokinetics
Dr. Mirza Ali, Statistics
Dr. Eduardo Abrao, Regulatory Affairs
Ms. Susan Welch, Regulatory Affairs
Dr. Daniel Gordin, Regulatory Affairs
Mr. Christopher Jones, Program Manager
Dr. Bimmie Strausser, OPC PDC

Topic: Aripiprazole (OPC-14597): February 19, 1997 End-of-Phase 2 Meeting

An End-of-Phase 2 meeting was held with the Division of Neuropharmacology, FDA to present the aripiprazole Phase 2 results and to discuss aripiprazole future clinical development. Dr. Daniel Gordin opened the meeting.

Dr. Jonathan Petrie followed and presented summaries of the aripiprazole pharmacology, pharmacokinetics, and the Phase 2 study results following which he presented for discussion the proposed pivotal study designs. The Division allowed the presentation to proceed without interruptions. Specific Otsuka questions were then presented by Dr. Gordin which covered issues pertaining to our future clinical development. The Otsuka questions are in bold followed by the FDA responses.

- 1. Is the proposed non-clinical program sufficient for initiating Phase 3 and adequate for an NDA filing?**

The FDA pharmacology reviewer indicated the following:

- The lack of toxicokinetic data to support the one year rat and monkey toxicology studies. The adequacy of the one year rat study was questioned in absence of toxicokinetic data; therefore, it was strongly recommended that this data be provided for evaluation.
- In order to compare toxicology studies, Otsuka needs to provide blood level data obtained from the two rat strains (Sprague Dawley and Fischer 344) which were used in the one year rat toxicology and rat carcinogenicity studies.
- Requested more information on the reproductive toxicology studies; specifically, the repeated Segment 2 rat fertility study (F1 female repeated study) and the Segment 3 rat peri- and post-natal studies.
- Requested delineation of target organ toxicity.
- Requested prolactin levels from the rat carcinogenicity study.
- Requested metabolic profile for the long term rat and monkey studies.
- Requested pharmacological data on the metabolites, depending upon activity.

- 2. An anesthetized dog study is planned to investigate further the effects of aripiprazole on the heart. Is this an acceptable model?**

The FDA indicated that if further cardiac effects are not seen in humans, then a study of this type would not be necessary.

- 3. Does the Division agree with the proposed PK studies?**

The FDA Biopharmaceutics reviewer indicated the following:

- The list of drugs for interaction studies may require modification depending on the metabolic pathways of aripiprazole.
- The determination of the absolute bioavailability of aripiprazole would be nice to know; however, the proposed relative bioavailability study is acceptable.
- The metabolism of aripiprazole in humans needs to be characterized.
- The list of proposed studies appeared to be adequate and requested that protocols be submitted for review and comment.
- If there are significant changes between the clinical and market formulations, then a bioequivalence study would be required.

- 4. Are the proposed Phase 3 study designs acceptable for supporting the indication, management of the manifestations of psychotic disorders, in regards to: patient inclusion criteria and classification, treatment arms, patient number, primary and secondary end points, study duration, and active comparators.**

The FDA medical reviewers indicated the following:

- The BPRS core (derived from PANSS) should be used as a primary endpoint in addition to the PANSS total and CGI severity scores. The BPRS scale will not be used as an instrument to measure patient symptoms; however, the BPRS-core score will be derived from PANSS.
- The dose and administration of the comparators (risperidone and haloperidol) used in the pivotal studies are not a concern of the Division and are at the Sponsor's discretion. The Division further pointed out that the use of a comparator is for validation of the study only.
- Inquired if Otsuka planned to stratify the patient population according to type of psychosis. Otsuka replied there were no plans to stratify since the numbers of schizoaffective and schizophreniform patients are very small.
- Inquired if Otsuka planned to conduct a long term relapse prevention study and studies in patients under the age of 18. Otsuka replied that it had no plans to conduct either a long term relapse prevention study or pediatric study and, as such, did not commit to include either study in the NDA.

- 5. The 30 mg dose has consistently been shown to be safe and effective for all instruments. Consequently, for the PI dosing section, we plan to pursue the recommendation "30 mg can be administered without titration". However, if the efficacy of 15 mg and/or 20 mg in their respective studies (Studies 97-201 and 97-202), compared to placebo, are no different from the efficacy of 30 mg compared to placebo, then what would be the possible impact on the proposed labeling dosing recommendation?**

The FDA medical reviewers indicated the following:

- The proposed study designs were acceptable for establishing dosing recommendations and commented on the fact that they will take into consideration all doses utilized in the clinical trials to write a descriptive dosing recommendation for the labeling.
- Expressed an interest in the safety of doses greater than 30 mg/day; however, indicated that it would be nice to know but was not a requirement.

- If Otsuka plans to show a difference between aripiprazole doses, the distribution of the effect size can be displayed in the package insert.
 - The time-to-discharge from the hospital endpoint appears to be a reasonable measure of clinical effectiveness and can be used to differentiate between doses.
- 6. Is the size of the proposed safety data base adequate?**
- Dr. Leber indicated that according to the ICH guidelines, Otsuka is expected to provide patients treated for at least six months should be 300 - 600.
 - With respect to the approximately 1600 total patient population that was proposed to the Division, Dr. Leber indicated that the more patients enrolled, the better.
- 7. Is the late Phase 2/3 Study 31-94-202 (Title: A Dose Ranging Study of Efficacy and Tolerability of Aripiprazole in Acutely Relapsing Hospitalized Schizophrenic Patients) which was double-blinded, 4 wk, randomized, well-controlled study in 307 male and female acute relapse schizophrenic patients (DSM-IV criteria) adequate to be accepted as a pivotal study?**
- The FDA medical review indicated that the Division will consider this study along with all other clinical studies that are submitted in the NDA.
- 8. In order to make claims of superiority or equivalence in the labeling, what type of comparator study design would be required?**
- Dr. Leber indicated the following:
- In terms of efficacy, it would be extremely difficult to obtain approval for a claim of superiority in the labeling.
 - In terms of safety, he indicated that if our maximum effective dose shows less occurrence of a side effect than the lowest dose of the comparator, then a superiority labeling claim for side effects may be acceptable.
- 9. Does the Division have any additional recommendations to support an approvable NDA?**
- Better characterization of the human and animal metabolic profile.
 - Define patient population adequately.

End-of-Phase 2 Meeting Minutes
February 19, 1997

Otsuka

- Quality of Japanese data should be high if the intent is to use it for a determination of safety and efficacy for the NDA and would thus, need to include translated case report forms, documentation of well-controlled studies, etc.
- If needed, meetings with the separate FDA review disciplines can be arranged.

APPEARS THIS WAY
ON ORIGINAL

OTSUKA MARYLAND RESEARCH INSTITUTE, LLC & BRISTOL MYERS SQUIBB CO.

FDA MEETING MINUTES

Division of Neuropharmacological Drug Products

**ARIPIRAZOLE
OPC-14597**

ORAL TABLET FORMULATION

**PreNDA Meeting
July 2, 2001**

Attendees from the Division of Neuropharmacological Drug Products, CDER, FDA:

Russell Katz, MD, Director
Tom Laughren, MD, Psychopharm Team Leader
Ni Khin, MD, Clinical Reviewer
Lois Freed, PhD, Pharm/Tox Reviewer
Barry Rosloff, PhD, Pharm/Tox Team Leader
Hong Zhao, Biopharm Reviewer
Judith Racoosin, MD, Safety Team Leader
Yuan-Li Shen, Statistician
Greg Dubitsky, MD, Clinical Reviewer
Kun Jin, PhD, Statistical Team Leader
Steve Hardeman, RPh, Senior Regulatory Project Manager

Attendees from Bristol Myers Squibb Company:

Donald Archibald, MPhil. - Director Clinical Biostatistics
William Carson, MD - Director Neuroscience Clinical Research & Development
Mark Dominick, DVM, PhD - Director, Pathology
Claude Nicaise, MD - VP Regulatory Science
Daniel Salazar, PhD - Director, Clinical Pharmacology
Laurie Smaldone, MD - Sr. VP Regulatory Science & Outcomes Research
Elyse Stock, MD - Group Director, Neuroscience Clinical Research & Development
Charles Wolleben, PhD - Director, Regulatory Science

Attendees from Otsuka Maryland Research Institute, LLC:

Kusuma Mallikaarjun, PhD - Associate Director, Regulatory Affairs
Mirza Ali, PhD - Director of Biostatistics

Attendees from Otsuka Pharmaceuticals Co. Ltd., Japan:

Taro Iwamoto, PhD - Global Project Leader
Kazumichi Kobayashi - Director, Medical Regulatory Affairs

Meeting Summary

Following introductions discussion began using the issues for discussion that were provided in the background document as an agenda for the meeting. The issues are provided below in italics followed by a summary of the ensuing discussion. To facilitate discussion a number of overheads were used to introduce each issue. These overheads are attached for reference.

Does the Division concur with the strategy laid out in the background document which would predict 15 mg/day as the recommended dose for aripiprazole in acute schizophrenia?

The Division commented that while the ultimate decision of dose will be driven by the data submitted in the NDA, given the information provided in the background document, the strategy proposed for determining the recommended dose seems reasonable. The strategy is based upon 1) the consistency of primary efficacy endpoints across studies, 2) the consistency of a variety of efficacy endpoints within studies, 3) the onset of efficacy, and 4) safety.

The evaluation of recommended dose in the Background and Overview of the Aripiprazole Program document includes a meta analysis of response by dose. Is such an evaluation helpful in the Division's assessment of the recommended dose?

FDA indicated that their decision would be primarily based on the individual study data. They would however take a look at the meta analysis since it has already been conducted.

Finally, we will be seeking concurrence with the Division regarding Dosage and Administration labeling similar to the following: The recommended dose is 15 mg/day, administered consistently as a single daily dose without regard to meals. Doses up to 30 mg/day have been shown to be safe and effective and can be used based upon individual clinical need.

The Division has no fundamental objection to including a dose higher than the recommended dose in labeling for those patients for which there may be some individual clinical need. They would reflect the dose response curve in the labeling. In response to a question from Dr. Katz, Dr. Stock indicated that there is no evidence that patients that do not respond appropriately at 15 mg improve when given 30 mg. Despite this Drs. Katz and Laughren indicated that doses up to 30 mg could be reflected in labeling as effective with the caveat that there is no evidence that this dose is more effective than 15 mg.

We believe that the adrenocortical findings reported from the supplemental two-year rat carcinogenicity study should be reflected in the carcinogenesis section of the label which would include a statement regarding the lack of relevance to humans. Does the Division concur with this assessment?

The Division informed us that they would simply reflect the data in labeling in the appropriate section. They commented that a statement regarding the lack of relevance to humans would not be appropriate unless the mechanism is a well proven/accepted one and it is also well established/accepted that this mechanism does not exist in humans.. Alternatively, labeling could reflect that the relevance of these findings to humans is unknown. Dr. Freed noted that while there is a 7-14 fold multiple of exposure between the doses at which adrenocortical carcinomas and pheochromocytomas were detected and the maximum expected human dose (30 mg), there is only approximately a 3 fold multiple between the no effect dose in the carcinogenicity study and the maximum expected human dose.

Does the Division concur with the assessment that the animal hepatobiliary data should be represented in an Animal Toxicology section of labeling which would include a statement that these findings are of questionable clinical relevance. No precautionary statement will be proposed regarding these findings.

To complement the data provided in the background document, the new human and in-vitro biliary solubility data was presented to the Agency. They inquired as to the duration of the human study and if the bile in this study was collected under standardized conditions, since bile formation is affected by numerous factors. With respect to assessing a signal in the human data base, Dr. Racoosin commented that we should cast a very wide net with regard to symptoms or adverse event terms to capture the complete picture of possible hepatobiliary findings in humans. For instance, all abdominal surgeries should be evaluated for possible links to gall stone involvement. Likewise, pancreatitis should be carefully evaluated. Dr. Racoosin also commented on the difficulty of picking up a signal via sonography due to the incidence of gall stones in the general population. With regard to the solubility of the individual metabolites in human bile, Dr. Katz speculated about the solubility of all three metabolites together in bile. Finally, Dr. Rosloff questioned the need to have this information reflected in labeling in the absence of a signal in humans and suggested that this might be excluded in its entirety. We were advised to make a strong case in our application for not including these data in labeling if we believe that the data are not relevant to humans.

Does the Division agree that the proposed QTc data analyses are adequate to assess the QTc effect of aripiprazole?

FDA informed us that they are comfortable with the analyses that have been done with respect to this issue. However, Dr. Racoosin provided us with their revised correction method for evaluating QTc which they expect us to apply to our data. They informed us that they are interested in outliers – anyone with >500 msec as well as all data available on QT, including data from uncontrolled, open label or extension trials as well as any long term data. They are interested in this data strictly to assess if there any “really bad things” occurring. They informed us that they want all data sets with regard to QTc and that they wish to know what will be presented in the NDA – e.g., the amount and duration of the data, methodologies and equipment used. We committed to providing a description of our complete ECG data set in the near future. FDA also informed us that they were interested in all our open label, long term study data even though these were uncontrolled. --Finally, they commented that labeling will reflect QTc data but negative statements can not be made in labeling for QTc.

Although FDA will not allow a statement that there is no QTc signal, they will remain silent if there is no QTc signal.

Does the Division agree with the incorporation of comparative safety data in final labeling?

The Agency will not allow such information in labeling unless we study equipotent doses of the comparators, in a prospectively defined manner. Placebo comparisons would be acceptable but no reference to active comparators data will be allowed in labeling.

Does the Division concur with proposal to provide data on positive and negative symptoms in labeling?

The Division informed us that they are open to this, there is already a precedent for this and that this should not be an issue. The data would be simply reflected in the clinical trials section of labeling. In general, when there has been precedent set for a particular area to be included in the label then statements could be included, even if regarding the absence of findings.

Does the Division agree with the proposal to provide a description of data from schizoaffective patients included in the clinical trial program in labeling?

No labeling statements regarding this population will be allowed unless we provided positive data from two prospectively designed trials in this population. When questioned whether or not a meta analysis involving the patients from the current program could be considered as one of the pivotal trails Drs. Katz and Laughren commented that they would be willing to review a meta analysis, even though such an analysis for this purpose was unusual in their opinion. Depending on the strength of the data, a single study proposal could be considered.

Will the Division allow the incorporation of pediatric pk data from study CN138-014 in final labeling?

This data will not be allowed in labeling due to the Agency's concern of off label promotion in the population. When asked if this data would not be consistent with the Agency's pediatric initiative efforts Dr. Katz pointed out that that the Pediatric Rule requires the collection of data in the pediatric population but does not require the inclusion of such data in labeling.

Does the Division concur that the format and content of the various components (e.g., CSR, ISS, ISE) of the NDA provided in the background package are adequate?

Dr Racoosin requested that we provide information in the ISS by indication. They would prefer to see the data separate first by indication and then pooled. She prefers that adverse event tables will be split by indication, unless the tables are identical. It is their belief that even though the two populations may appear identical, the schizophrenic patients are more pre-disposed to cardiovascular problems and hyperglycemia. There is no such suggestion that this is the case for mania patients. They are not concerned about the usual adverse events but are focused on the serious and rare events that may differ between the two populations. They will decide the validity of our proposal to pool the two indications in labeling following their review. They informed us that each population should also be further analyzed for age, gender, race, and etc. differences. When informed that this would result in very small data sets, they asked us to present

these additional data cuts based on what would make sense. Dr Racoosin also provided written comments regarding the ISS in the briefing package. These comments included the preferred method for evaluation of glucose metabolism.

The Division requested that we provide them a clear interpretation/map for the COSTART terms. They requested us to make sure that our narratives were adequately detailed and not just sentences cut and pasted from CRFs. Both the COSTART terms and the narratives have to be totally transparent.

Dr. Zhao requested that we include the in vitro metabolism results in Section 6 of the NDA as well as the preclinical section.

When asked how they would like to have the US vs non-US data displayed/evaluated, the Division commented that they will evaluate differences, if any, between these geographic populations based on information in the individual study reports. No further analyses are required at this stage.

Are the data sets listed in the proposal for the electronic components of the NDA acceptable to the Division's review team?

The proposal for the data sets and the variables to be provided was adequate, but in addition the Division is most interested in receiving all safety data sets electronically. There is no need to provide efficacy data sets for the pilot studies and the open label extension studies. A Safety data set should be provided which contains data from all studies including pilot studies and open label extensions.

The importance of ensuring that the unique patient identification numbers were the same between the short term and long term studies to enable them to track/follow a patient with adverse events when rolled into a long term study was highlighted.

In response to a question from Dr. Freed, we informed her that we were not intending to provide any of the pharm/tox section of the NDA as a Part 11 compliant electronic file. However, we would follow up with her to see what we could provide electronically to facilitate her review and assessment of this section of the NDA.