

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***

**NDA 21-436/S-001**

***Trade Name:*** Abilify Tablets

***Generic Name:*** Aripiprazole

***Sponsor:*** Otsuka America Pharmaceutical, Inc. and  
Bristol-Myers Squibb Company

***Approval Date:*** 8/28/03

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*APPLICATION NUMBER:*  
**NDA 21-436/S-001**

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*APPLICATION NUMBER:*

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**APPROVAL LETTER**



NDA 21-436 / S-001

Otsuka America Pharmaceutical, Inc.  
Attention: Kusuma Mallikaarjun, Ph.D.  
2440 Research Boulevard  
Rockville, MD 20850

Dear Dr. Mallikaarjun:

Please refer to your supplemental new drug application dated December 3, 2002, received December 4, 2002, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Abilify (aripiprazole) Tablets.

We acknowledge receipt of your submissions of February 12, 2003, February 20, 2003, March 28, 2003, August 7, 2003, and August 12, 2003.

This supplemental new drug application (supplement) provides for the longer-term efficacy of aripiprazole in the treatment of schizophrenia.

We have completed our review of this application, as amended and it is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text (email of August 28, 2003).

#### **Postmarketing Study Commitment**

This supplement also provides for the fulfillment of the following post approval commitment:

- (Study 5)  
Submit the results of Study CN138-047 (A Multicenter, Randomized, Double-Blind, Placebo Controlled, 26 Week Study Of A Fixed Dose Of Aripiprazole In The Treatment Of Stabilized Patients With Chronic Schizophrenia) to address the longer-term efficacy of aripiprazole in the treatment of adults with schizophrenia.

The above commitment has now been fulfilled.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert).

Please submit the FPL electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – NDA. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount 15 of the copies on heavy weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 21-436 / S-001". Approval of this submission by FDA is not required before the labeling is used.

FDA's Pediatric Rule [at 21 CFR 314.55/21 CFR 601.27] was challenged in court. On October 17, 2002, the court ruled that FDA did not have the authority to issue the Pediatric Rule and has barred FDA from enforcing it. Although the government decided not to pursue an appeal in the courts, it will work with Congress in an effort to enact legislation requiring pharmaceutical manufacturers to conduct appropriate pediatric clinical trials. In addition, third party interveners have decided to appeal the court's decision striking down the rule. Therefore, we encourage you to submit a pediatric plan that describes development of your product in the pediatric population where it may be used. Please be aware that whether or not this pediatric plan and subsequent submission of pediatric data will be required depends upon passage of legislation or the success of the third party appeal. In any event, we hope you will decide to submit a pediatric plan and conduct the appropriate pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

The pediatric exclusivity provisions of FDAMA as reauthorized by the Best Pharmaceuticals for Children Act are not affected by the court's ruling. 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. Please refer to the Agency's Pediatric Written Request letter of February 11, 2003, for further details.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HFD-410  
FDA  
5600 Fishers Lane  
Rockville, MD 20857

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

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

Enclosure (labeling)

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

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Russell Katz  
8/28/03 01:51:08 PM

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*APPLICATION NUMBER:*  
**NDA 21-436/S-001**

**LABELING**

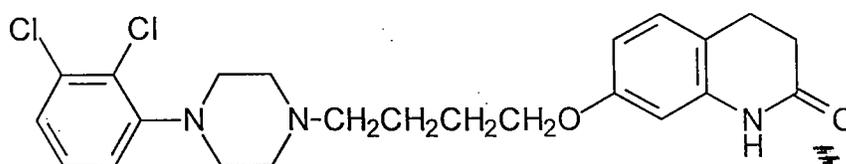
**ABILIFY™**

**Rx only**

**(aripiprazole) Tablets**

## DESCRIPTION

ABILIFY™ (aripiprazole) is a psychotropic drug that is available as tablets for oral administration. Aripiprazole is 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydrocarbostyrl. The empirical formula is  $C_{23}H_{27}Cl_2N_3O_2$  and its molecular weight is 448.38. The chemical structure is:



ABILIFY tablets are available in 5-mg, 10-mg, 15-mg, 20-mg, and 30-mg strengths. Inactive ingredients include lactose monohydrate, cornstarch, microcrystalline cellulose, hydroxypropyl cellulose, and magnesium stearate. Colorants include ferric oxide (yellow or red) and FD&C Blue No. 2 Aluminum Lake.

## CLINICAL PHARMACOLOGY

### Pharmacodynamics

Aripiprazole exhibits high affinity for dopamine  $D_2$  and  $D_3$ , serotonin  $5-HT_{1A}$  and  $5-HT_{2A}$  receptors ( $K_i$  values of 0.34, 0.8, 1.7, and 3.4 nM, respectively), moderate affinity for dopamine  $D_4$ , serotonin  $5-HT_{2C}$  and  $5-HT_7$ ,  $\alpha_1$ -adrenergic and histamine  $H_1$  receptors ( $K_i$  values of 44, 15, 39, 57, and 61 nM, respectively), and moderate affinity for the serotonin reuptake site ( $K_i=98$  nM). Aripiprazole has no appreciable affinity for cholinergic muscarinic receptors ( $IC_{50}>1000$  nM). Aripiprazole functions as a partial agonist at the dopamine  $D_2$  and the serotonin  $5-HT_{1A}$  receptors, and as an antagonist at serotonin  $5-HT_{2A}$  receptor.

The mechanism of action of aripiprazole, as with other drugs having efficacy in schizophrenia, is unknown. However, it has been proposed that the efficacy of aripiprazole is mediated through a combination of partial agonist activity at  $D_2$  and  $5-HT_{1A}$  receptors and antagonist activity at  $5-HT_{2A}$  receptors. Actions at receptors other than  $D_2$ ,  $5-HT_{1A}$ , and  $5-HT_{2A}$  may explain some of the other clinical effects of

aripiprazole, eg, the orthostatic hypotension observed with aripiprazole may be explained by its antagonist activity at adrenergic  $\alpha_1$  receptors.

## Pharmacokinetics

ABILIFY activity is presumably primarily due to the parent drug, aripiprazole, and to a lesser extent, to its major metabolite, dehydro-aripiprazole, which has been shown to have affinities for  $D_2$  receptors similar to the parent drug and represents 40% of the parent drug exposure in plasma. The mean elimination half-lives are about 75 hours and 94 hours for aripiprazole and dehydro-aripiprazole, respectively. Steady-state concentrations are attained within 14 days of dosing for both active moieties. Aripiprazole accumulation is predictable from single-dose pharmacokinetics. At steady state, the pharmacokinetics of aripiprazole are dose-proportional. Elimination of aripiprazole is mainly through hepatic metabolism involving two P450 isozymes, CYP2D6 and CYP3A4.

## Absorption

Aripiprazole is well absorbed, with peak plasma concentrations occurring within 3 to 5 hours; the absolute oral bioavailability of the tablet formulation is 87%. ABILIFY can be administered with or without food. Administration of a 15-mg ABILIFY tablet with a standard high-fat meal did not significantly affect the  $C_{max}$  or AUC of aripiprazole or its active metabolite, dehydro-aripiprazole, but delayed  $T_{max}$  by 3 hours for aripiprazole and 12 hours for dehydro-aripiprazole.

## Distribution

The steady-state volume of distribution of aripiprazole following intravenous administration is high (404 L or 4.9 L/kg), indicating extensive extravascular distribution. At therapeutic concentrations, aripiprazole and its major metabolite are greater than 99% bound to serum proteins, primarily to albumin. In healthy human volunteers administered 0.5 to 30 mg/day aripiprazole for 14 days, there was dose-dependent  $D_2$ -receptor occupancy indicating brain penetration of aripiprazole in humans.

## Metabolism and Elimination

Aripiprazole is metabolized primarily by three biotransformation pathways: dehydrogenation, hydroxylation, and N-dealkylation. Based on *in vitro* studies, CYP3A4 and CYP2D6 enzymes are responsible for dehydrogenation and hydroxylation of

aripiprazole, and N-dealkylation is catalyzed by CYP3A4. Aripiprazole is the predominant drug moiety in the systemic circulation. At steady state, dehydro-aripiprazole, the active metabolite, represents about 40% of aripiprazole AUC in plasma.

Approximately 8% of Caucasians lack the capacity to metabolize CYP2D6 substrates and are classified as poor metabolizers (PM), whereas the rest are extensive metabolizers (EM). PMs have about an 80% increase in aripiprazole exposure and about a 30% decrease in exposure to the active metabolite compared to EMs, resulting in about a 60% higher exposure to the total active moieties from a given dose of aripiprazole compared to EMs. Coadministration of ABILIFY with known inhibitors of CYP2D6, like quinidine in EMs, results in a 112% increase in aripiprazole plasma exposure, and dosing adjustment is needed (see **PRECAUTIONS: Drug-Drug Interactions**). The mean elimination half-lives are about 75 hours and 146 hours for aripiprazole in EMs and PMs, respectively. Aripiprazole does not inhibit or induce the CYP2D6 pathway.

Following a single oral dose of [<sup>14</sup>C]-labeled aripiprazole, approximately 25% and 55% of the administered radioactivity was recovered in the urine and feces, respectively. Less than 1% of unchanged aripiprazole was excreted in the urine and approximately 18% of the oral dose was recovered unchanged in the feces.

## Special Populations

In general, no dosage adjustment for ABILIFY is required on the basis of a patient's age, gender, race, smoking status, hepatic function, or renal function (see **DOSAGE AND ADMINISTRATION: Dosage in Special Populations**). The pharmacokinetics of aripiprazole in special populations are described below.

### Hepatic Impairment

In a single-dose study (15 mg of aripiprazole) in subjects with varying degrees of liver cirrhosis (Child-Pugh Classes A, B, and C), the AUC of aripiprazole, compared to healthy subjects, increased 31% in mild HI, increased 8% in moderate HI, and decreased 20% in severe HI. None of these differences would require dose adjustment.

### Renal Impairment

In patients with severe renal impairment (creatinine clearance <30 mL/min), C<sub>max</sub> of aripiprazole (given in a single dose of 15 mg) and dehydro-aripiprazole increased by 36% and 53%, respectively, but AUC was 15% lower for aripiprazole and 7% higher for

dehydro-aripiprazole. Renal excretion of both unchanged aripiprazole and dehydro-aripiprazole is less than 1% of the dose. No dosage adjustment is required in subjects with renal impairment.

### **Elderly**

In formal single-dose pharmacokinetic studies (with aripiprazole given in a single dose of 15 mg), aripiprazole clearance was 20% lower in elderly ( $\geq 65$  years) subjects compared to younger adult subjects (18 to 64 years). There was no detectable age effect, however, in the population pharmacokinetic analysis in schizophrenia patients. Also, the pharmacokinetics of aripiprazole after multiple doses in elderly patients appeared similar to that observed in young, healthy subjects. No dosage adjustment is recommended for elderly patients (see **PRECAUTIONS: Geriatric Use**).

### **Gender**

$C_{max}$  and AUC of aripiprazole and its active metabolite, dehydro-aripiprazole, are 30 to 40% higher in women than in men, and correspondingly, the apparent oral clearance of aripiprazole is lower in women. These differences, however, are largely explained by differences in body weight (25%) between men and women. No dosage adjustment is recommended based on gender.

### **Race**

Although no specific pharmacokinetic study was conducted to investigate the effects of race on the disposition of aripiprazole, population pharmacokinetic evaluation revealed no evidence of clinically significant race-related differences in the pharmacokinetics of aripiprazole. No dosage adjustment is recommended based on race.

### **Smoking**

Based on studies utilizing human liver enzymes *in vitro*, aripiprazole is not a substrate for CYP1A2 and also does not undergo direct glucuronidation. Smoking should, therefore, not have an effect on the pharmacokinetics of aripiprazole. Consistent with these *in vitro* results, population pharmacokinetic evaluation did not reveal any significant pharmacokinetic differences between smokers and nonsmokers. No dosage adjustment is recommended based on smoking status.

## Drug-Drug Interactions

### Potential for Other Drugs to Affect ABILIFY

Aripiprazole is not a substrate of CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2E1 enzymes. Aripiprazole also does not undergo direct glucuronidation. This suggests that an interaction of aripiprazole with inhibitors or inducers of these enzymes, or other factors, like smoking, is unlikely.

Both CYP3A4 and CYP2D6 are responsible for aripiprazole metabolism. Agents that induce CYP3A4 (eg, carbamazepine) could cause an increase in aripiprazole clearance and lower blood levels. Inhibitors of CYP3A4 (eg, ketoconazole) or CYP2D6 (eg, quinidine, fluoxetine, or paroxetine) can inhibit aripiprazole elimination and cause increased blood levels.

### Potential for ABILIFY to Affect Other Drugs

Aripiprazole is unlikely to cause clinically important pharmacokinetic interactions with drugs metabolized by cytochrome P450 enzymes. In *in vivo* studies, 10- to 30-mg/day doses of aripiprazole had no significant effect on metabolism by CYP2D6 (dextromethorphan), CYP2C9 (warfarin), CYP2C19 (omeprazole, warfarin), and CYP3A4 (dextromethorphan) substrates. Additionally, aripiprazole and dehydro-aripiprazole did not show potential for altering CYP1A2-mediated metabolism *in vitro* (see **PRECAUTIONS: Drug-Drug Interactions**).

*Aripiprazole had no clinically important interactions with the following drugs:*

*Famotidine:* Coadministration of aripiprazole (given in a single dose of 15 mg) with a 40-mg single dose of the H<sub>2</sub> antagonist famotidine, a potent gastric acid blocker, decreased the solubility of aripiprazole and, hence, its rate of absorption, reducing by 37% and 21% the C<sub>max</sub> of aripiprazole and dehydro-aripiprazole, respectively, and by 13% and 15%, respectively, the extent of absorption (AUC). No dosage adjustment of aripiprazole is required when administered concomitantly with famotidine.

*Valproate:* When valproate (500-1500 mg/day) and aripiprazole (30 mg/day) were coadministered at steady state, the C<sub>max</sub> and AUC of aripiprazole were decreased by 25%. No dosage adjustment of aripiprazole is required when administered concomitantly with valproate.

*Lithium:* A pharmacokinetic interaction of aripiprazole with lithium is unlikely because lithium is not bound to plasma proteins, is not metabolized, and is almost entirely excreted unchanged in urine. Coadministration of therapeutic doses of lithium (1200-1800 mg/day) for 21 days with aripiprazole (30 mg/day) did not result in clinically significant changes in the pharmacokinetics of aripiprazole or its active metabolite, dehydro-aripiprazole (C<sub>max</sub> and AUC increased by less than 20%). No dosage adjustment of aripiprazole is required when administered concomitantly with lithium.

*Dextromethorphan:* Aripiprazole at doses of 10 to 30 mg per day for 14 days had no effect on dextromethorphan's O-dealkylation to its major metabolite, dextrophan, a pathway known to be dependent on CYP2D6 activity. Aripiprazole also had no effect on dextromethorphan's N-demethylation to its metabolite 3-methoxymorphan, a pathway known to be dependent on CYP3A4 activity. No dosage adjustment of dextromethorphan is required when administered concomitantly with aripiprazole.

*Warfarin:* Aripiprazole 10 mg per day for 14 days had no effect on the pharmacokinetics of R- and S-warfarin or on the pharmacodynamic end point of International Normalized Ratio, indicating the lack of a clinically relevant effect of aripiprazole on CYP2C9 and CYP2C19 metabolism or the binding of highly protein-bound warfarin. No dosage adjustment of warfarin is required when administered concomitantly with aripiprazole.

*Omeprazole:* Aripiprazole 10 mg per day for 15 days had no effect on the pharmacokinetics of a single 20-mg dose of omeprazole, a CYP2C19 substrate, in healthy subjects. No dosage adjustment of omeprazole is required when administered concomitantly with aripiprazole.

## **Clinical Studies**

The efficacy of ABILIFY in the treatment of schizophrenia was evaluated in four short-term (4- and 6-week), placebo-controlled trials of acutely relapsed inpatients who predominantly met DSM-III/IV criteria for schizophrenia. Three of the four trials were able to distinguish aripiprazole from placebo, but one study, the smallest, did not. Three of these studies also included an active control group consisting of either risperidone (one trial) or haloperidol (two trials), but they were not designed to allow for a comparison of ABILIFY and the active comparators.

In the three positive trials for ABILIFY, four primary measures were used for assessing psychiatric signs and symptoms. The Positive and Negative Syndrome Scale

(PANSS) is a multi-item inventory of general psychopathology used to evaluate the effects of drug treatment in schizophrenia. The PANSS positive subscale is a subset of items in the PANSS that rates seven positive symptoms of schizophrenia (delusions, conceptual disorganization, hallucinatory behavior, excitement, grandiosity, suspiciousness/persecution, and hostility). The PANSS negative subscale is a subset of items in the PANSS that rates seven negative symptoms of schizophrenia (blunted affect, emotional withdrawal, poor rapport, passive apathetic withdrawal, difficulty in abstract thinking, lack of spontaneity/flow of conversation, stereotyped thinking). The Clinical Global Impression (CGI) assessment reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient.

In a 4-week trial (n=414) comparing two fixed doses of ABILIFY (15 or 30 mg/day) and haloperidol (10 mg/day) to placebo, both doses of ABILIFY were superior to placebo in the PANSS total score, PANSS positive subscale, and CGI-severity score. In addition, the 15-mg dose was superior to placebo in the PANSS negative subscale.

In a 4-week trial (n=404) comparing two fixed doses of ABILIFY (20 or 30 mg/day) and risperidone (6 mg/day) to placebo, both doses of ABILIFY were superior to placebo in the PANSS total score, PANSS positive subscale, PANSS negative subscale, and CGI-severity score.

In a 6-week trial (n=420) comparing three fixed doses of ABILIFY (10, 15, or 20 mg/day) to placebo, all three doses of ABILIFY were superior to placebo in the PANSS total score, PANSS positive subscale, and the PANSS negative subscale.

In a fourth study, a 4-week trial (n=103) comparing ABILIFY in a range of 5 to 30 mg/day or haloperidol 5 to 20 mg/day to placebo, haloperidol was superior to placebo, in the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general psychopathology traditionally used to evaluate the effects of drug treatment in psychosis, and in a responder analysis based on the CGI-severity score, the primary outcomes for that trial. ABILIFY was only significantly different compared to placebo in a responder analysis based on the CGI-severity score.

Thus, the efficacy of 15-mg, 20-mg, and 30-mg daily doses was established in two studies for each dose, whereas the efficacy of the 10-mg dose was established in one study. There was no evidence in any study that the higher dose groups offered any advantage over the lowest dose group.

An examination of population subgroups did not reveal any clear evidence of differential responsiveness on the basis of age, gender, or race.

A longer-term trial enrolled 310 inpatients or outpatients meeting DSM-IV criteria for schizophrenia who were, by history, symptomatically stable on other antipsychotic medications for periods of 3 months or longer. These patients were discontinued from their antipsychotic medications and randomized to ABILIFY 15 mg or placebo for up to 26 weeks of observation for relapse. Relapse during the double-blind phase was defined as CGI-Improvement score of  $\geq 5$  (minimally worse), scores  $\geq 5$  (moderately severe) on the hostility or uncooperativeness items of the PANSS, or  $\geq 20\%$  increase in the PANSS Total score. Patients receiving ABILIFY 15 mg experienced a significantly longer time to relapse over the subsequent 26 weeks compared to those receiving placebo.

## **INDICATIONS AND USAGE**

ABILIFY is indicated for the treatment of schizophrenia. The efficacy of ABILIFY in the treatment of schizophrenia was established in short-term (4- and 6-week) controlled trials of schizophrenic inpatients (see **CLINICAL PHARMACOLOGY: Clinical Studies**).

The efficacy of ABILIFY in maintaining stability in patients with schizophrenia who had been symptomatically stable on other antipsychotic/medications for periods of 3 months or longer, were discontinued from those other medications, and were then administered ABILIFY 15 mg/day and observed for relapse during a period of up to 26 weeks was demonstrated in a placebo-controlled trial (see **CLINICAL PHARMACOLOGY: Clinical Studies**). The physician who elects to use ABILIFY for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see **DOSAGE AND ADMINISTRATION**).

## **CONTRAINDICATIONS**

ABILIFY is contraindicated in patients with a known hypersensitivity to the product.

## **WARNINGS**

### **Neuroleptic Malignant Syndrome (NMS)**

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic

drugs, including aripiprazole. Two possible cases of NMS occurred during aripiprazole treatment in the premarketing worldwide clinical database. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (eg, pneumonia, systemic infection, etc) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

## **Tardive Dyskinesia**

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and, thereby, may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, ABILIFY should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on ABILIFY, drug discontinuation should be considered. However, some patients may require treatment with ABILIFY despite the presence of the syndrome.

## **PRECAUTIONS**

### **General**

#### **Orthostatic Hypotension**

Aripiprazole may be associated with orthostatic hypotension, perhaps due to its  $\alpha_1$ -adrenergic receptor antagonism. The incidence of orthostatic hypotension associated events from five short-term, placebo-controlled trials in schizophrenia (n=926) on ABILIFY included: orthostatic hypotension (placebo 1%, aripiprazole 1.9%), orthostatic lightheadedness (placebo 1%, aripiprazole 0.9%), and syncope (placebo 1%, aripiprazole 0.6%). The incidence of a significant orthostatic change in blood pressure (defined as a decrease of at least 30 mmHg in systolic blood pressure when changing from a supine to standing position) for aripiprazole was not statistically different from placebo (14% among aripiprazole-treated patients and 12% among placebo-treated patients).

Aripiprazole should be used with caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease, or conditions which would

predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications).

### **Seizure**

Seizures occurred in 0.1% (1/926) of aripiprazole-treated patients in short-term, placebo-controlled trials. As with other antipsychotic drugs, aripiprazole should be used cautiously in patients with a history of seizures or with conditions that lower the seizure threshold, eg, Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

### **Potential for Cognitive and Motor Impairment**

In short-term, placebo-controlled trials, somnolence was reported in 11% of patients on ABILIFY compared to 8% of patients on placebo; somnolence led to discontinuation in 0.1% (1/926) of patients on ABILIFY in short-term, placebo-controlled trials. Despite the relatively modest increased incidence of somnolence compared to placebo, ABILIFY, like other antipsychotics, may have the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that therapy with ABILIFY does not affect them adversely.

### **Body Temperature Regulation**

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing aripiprazole for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, eg, exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

### **Dysphagia**

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. Aripiprazole and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia (see **PRECAUTIONS: Use in Patients with Concomitant Illness**).

## Suicide

The possibility of a suicide attempt is inherent in psychotic illnesses, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for ABILIFY should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

## Use in Patients with Concomitant Illness

*Safety Experience in Elderly Patients with Psychosis Associated with Alzheimer's Disease:* In a flexible dose (2 to 15 mg/day), 10-week, placebo-controlled study of aripiprazole in elderly patients (mean age: 81.5 years; range: 56 to 95 years) with psychosis associated with Alzheimer's dementia, 4 of 105 patients (3.8%) who received ABILIFY died compared to no deaths among 102 patients who received placebo during or within 30 days after termination of the double-blind portion of the study. Three of the patients (age 92, 91, and 87 years) died following the discontinuation of ABILIFY in the double-blind phase of the study (causes of death were pneumonia, heart failure, and shock). The fourth patient (age 78 years) died following hip surgery while in the double-blind portion of the study. The treatment-emergent adverse events that were reported at an incidence of  $\geq 5\%$  and having a greater incidence than placebo in this study were accidental injury, somnolence, and bronchitis. Eight percent of the ABILIFY-treated patients reported somnolence compared to one percent of placebo patients. In a small pilot, open-label, ascending-dose, cohort study (n=30) in elderly patients with dementia, ABILIFY was associated in a dose-related fashion with somnolence.

The safety and efficacy of ABILIFY in the treatment of patients with psychosis associated with dementia have not been established. If the prescriber elects to treat such patients with ABILIFY, vigilance should be exercised, particularly for the emergence of difficulty swallowing or excessive somnolence, which could predispose to accidental injury or aspiration.

Clinical experience with ABILIFY in patients with certain concomitant systemic illnesses (see **CLINICAL PHARMACOLOGY: Special Populations: Renal Impairment and Hepatic Impairment**) is limited.

ABILIFY has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies.

## **Information for Patients**

Physicians are advised to discuss the following issues with patients for whom they prescribe ABILIFY:

### **Interference with Cognitive and Motor Performance**

Because aripiprazole may have the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that aripiprazole therapy does not affect them adversely.

### **Pregnancy**

Patients should be advised to notify their physician if they become pregnant ~~or~~ intend to become pregnant during therapy with ABILIFY.

### **Nursing**

Patients should be advised not to breast-feed an infant if they are taking ABILIFY.

### **Concomitant Medication**

Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions.

### **Alcohol**

Patients should be advised to avoid alcohol while taking ABILIFY.

### **Heat Exposure and Dehydration**

Patients should be advised regarding appropriate care in avoiding overheating and dehydration.

### **Drug-Drug Interactions**

Given the primary CNS effects of aripiprazole, caution should be used when ABILIFY is taken in combination with other centrally acting drugs and alcohol. Due to its  $\alpha_1$ -

adrenergic receptor antagonism, aripiprazole has the potential to enhance the effect of certain antihypertensive agents.

### **Potential for Other Drugs to Affect ABILIFY**

Aripiprazole is not a substrate of CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2E1 enzymes. Aripiprazole also does not undergo direct glucuronidation. This suggests that an interaction of aripiprazole with inhibitors or inducers of these enzymes, or other factors, like smoking, is unlikely.

Both CYP3A4 and CYP2D6 are responsible for aripiprazole metabolism. Agents that induce CYP3A4 (eg, carbamazepine) could cause an increase in aripiprazole clearance and lower blood levels. Inhibitors of CYP3A4 (eg, ketoconazole) or CYP2D6 (eg, quinidine, fluoxetine, or paroxetine) can inhibit aripiprazole elimination and cause increased blood levels.

*Ketoconazole:* Coadministration of ketoconazole (200 mg/day for 14 days) with a 15-mg single dose of aripiprazole increased the AUC of aripiprazole and its active metabolite by 63% and 77%, respectively. The effect of a higher ketoconazole dose (400 mg/day) has not been studied. When concomitant administration of ketoconazole with aripiprazole occurs, aripiprazole dose should be reduced to one-half of its normal dose. Other strong inhibitors of CYP3A4 (itraconazole) would be expected to have similar effects and need similar dose reductions; weaker inhibitors (erythromycin, grapefruit juice) have not been studied. When the CYP3A4 inhibitor is withdrawn from the combination therapy, aripiprazole dose should then be increased.

*Quinidine:* Coadministration of a 10-mg single dose of aripiprazole with quinidine (166 mg/day for 13 days), a potent inhibitor of CYP2D6, increased the AUC of aripiprazole by 112% but decreased the AUC of its active metabolite, dehydro-aripiprazole, by 35%. Aripiprazole dose should be reduced to one-half of its normal dose when concomitant administration of quinidine with aripiprazole occurs. Other significant inhibitors of CYP2D6, such as fluoxetine or paroxetine, would be expected to have similar effects and, therefore, should be accompanied by similar dose reductions. When the CYP2D6 inhibitor is withdrawn from the combination therapy, aripiprazole dose should then be increased.

*Carbamazepine:* Coadministration of carbamazepine (200 mg BID), a potent CYP3A4 inducer, with aripiprazole (30 mg QD) resulted in an approximate 70% decrease in C<sub>max</sub> and AUC values of both aripiprazole and its active metabolite,

dehydro-aripiprazole. When carbamazepine is added to aripiprazole therapy, aripiprazole dose should be doubled. Additional dose increases should be based on clinical evaluation. When carbamazepine is withdrawn from the combination therapy, aripiprazole dose should then be reduced.

No clinically significant effect of famotidine, valproate, or lithium was seen on the pharmacokinetics of aripiprazole (see **CLINICAL PHARMACOLOGY: Drug-Drug Interactions**).

### **Potential for ABILIFY to Affect Other Drugs**

Aripiprazole is unlikely to cause clinically important pharmacokinetic interactions with drugs metabolized by cytochrome P450 enzymes. In *in vivo* studies, 10- to 30-mg/day doses of aripiprazole had no significant effect on metabolism by CYP2D6 (dextromethorphan), CYP2C9 (warfarin), CYP2C19 (omeprazole, warfarin), and CYP3A4 (dextromethorphan) substrates. Additionally, aripiprazole and dehydro-aripiprazole did not show potential for altering CYP1A2-mediated metabolism *in vitro* (see **CLINICAL PHARMACOLOGY: Drug-Drug Interactions**).

*Alcohol:* There was no significant difference between aripiprazole coadministered with ethanol and placebo coadministered with ethanol on performance of gross motor skills or stimulus response in healthy subjects. As with most psychoactive medications, patients should be advised to avoid alcohol while taking ABILIFY.

## **Carcinogenesis, Mutagenesis, Impairment of Fertility**

### **Carcinogenesis**

Lifetime carcinogenicity studies were conducted in ICR mice and in Sprague-Dawley (SD) and F344 rats. Aripiprazole was administered for 2 years in the diet at doses of 1, 3, 10, and 30 mg/kg/day to ICR mice and 1, 3, and 10 mg/kg/day to F344 rats (0.2 to 5 and 0.3 to 3 times the maximum recommended human dose [MRHD] based on mg/m<sup>2</sup>, respectively). In addition, SD rats were dosed orally for 2 years at 10, 20, 40, and 60 mg/kg/day (3 to 19 times the MRHD based on mg/m<sup>2</sup>). Aripiprazole did not induce tumors in male mice or rats. In female mice, the incidences of pituitary gland adenomas and mammary gland adenocarcinomas and adenoacanthomas were increased at dietary doses of 3 to 30 mg/kg/day (0.1 to 0.9 times human exposure at MRHD based on AUC and 0.5 to 5 times the MRHD based on mg/m<sup>2</sup>). In female rats, the incidence of mammary gland fibroadenomas was increased at a dietary dose of 10 mg/kg/day (0.1

times human exposure at MRHD based on AUC and 3 times the MRHD based on  $\text{mg}/\text{m}^2$ ); and the incidences of adrenocortical carcinomas and combined adrenocortical adenomas/carcinomas were increased at an oral dose of 60  $\text{mg}/\text{kg}/\text{day}$  (14 times human exposure at MRHD based on AUC and 19 times the MRHD based on  $\text{mg}/\text{m}^2$ ).

Proliferative changes in the pituitary and mammary gland of rodents have been observed following chronic administration of other antipsychotic agents and are considered prolactin-mediated. Serum prolactin was not measured in the aripiprazole carcinogenicity studies. However, increases in serum prolactin levels were observed in female mice in a 13-week dietary study at the doses associated with mammary gland and pituitary tumors. Serum prolactin was not increased in female rats in 4- and 13-week dietary studies at the dose associated with mammary gland tumors. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown.

### **Mutagenesis**

The mutagenic potential of aripiprazole was tested in the *in vitro* bacterial reverse-mutation assay, the *in vitro* bacterial DNA repair assay, the *in vitro* forward gene mutation assay in mouse lymphoma cells, the *in vitro* chromosomal aberration assay in Chinese hamster lung (CHL) cells, the *in vivo* micronucleus assay in mice, and the unscheduled DNA synthesis assay in rats. Aripiprazole and a metabolite (2,3-DCPP) were clastogenic in the *in vitro* chromosomal aberration assay in CHL cells with and without metabolic activation. The metabolite, 2,3-DCPP, produced increases in numerical aberrations in the *in vitro* assay in CHL cells in the absence of metabolic activation. A positive response was obtained in the *in vivo* micronucleus assay in mice, however, the response was shown to be due to a mechanism not considered relevant to humans.

### **Impairment of Fertility**

Female rats were treated with oral doses of 2, 6, and 20  $\text{mg}/\text{kg}/\text{day}$  (0.6, 2, and 6 times the maximum recommended human dose [MRHD] on a  $\text{mg}/\text{m}^2$  basis) of aripiprazole from 2 weeks prior to mating through day 7 of gestation. Estrus cycle irregularities and increased corpora lutea were seen at all doses, but no impairment of fertility was seen. Increased pre-implantation loss was seen at 6 and 20  $\text{mg}/\text{kg}$ , and decreased fetal weight was seen at 20  $\text{mg}/\text{kg}$ .

Male rats were treated with oral doses of 20, 40, and 60  $\text{mg}/\text{kg}/\text{day}$  (6, 13, and 19 times the MRHD on a  $\text{mg}/\text{m}^2$  basis) of aripiprazole from 9 weeks prior to mating through

mating. Disturbances in spermatogenesis were seen at 60 mg/kg, and prostate atrophy was seen at 40 and 60 mg/kg, but no impairment of fertility was seen.

## **Pregnancy**

### **Pregnancy Category C**

In animal studies, aripiprazole demonstrated developmental toxicity, including possible teratogenic effects in rats and rabbits.

Pregnant rats were treated with oral doses of 3, 10, and 30 mg/kg/day (1, 3, and 10 times the maximum recommended human dose [MRHD] on a  $\text{mg}/\text{m}^2$  basis) of aripiprazole during the period of organogenesis. Gestation was slightly prolonged at 30 mg/kg. Treatment caused a slight delay in fetal development, as evidenced by decreased fetal weight (30 mg/kg), undescended testes (30 mg/kg), and delayed skeletal ossification (10 and 30 mg/kg). There were no adverse effects on embryofetal or pup survival. Delivered offspring had decreased bodyweights (10 and 30 mg/kg), and increased incidences of hepatodiaphragmatic nodules and diaphragmatic hernia at 30 mg/kg (the other dose groups were not examined for these findings). (A low incidence of diaphragmatic hernia was also seen in the fetuses exposed to 30 mg/kg.) Postnatally, delayed vaginal opening was seen at 10 and 30 mg/kg and impaired reproductive performance (decreased fertility rate, corpora lutea, implants, and live fetuses, and increased post-implantation loss, likely mediated through effects on female offspring) was seen at 30 mg/kg. Some maternal toxicity was seen at 30 mg/kg, however, there was no evidence to suggest that these developmental effects were secondary to maternal toxicity.

Pregnant rabbits were treated with oral doses of 10, 30, and 100 mg/kg/day (2, 3, and 11 times human exposure at MRHD based on AUC and 6, 19, and 65 times the MRHD based on  $\text{mg}/\text{m}^2$ ) of aripiprazole during the period of organogenesis. Decreased maternal food consumption and increased abortions were seen at 100 mg/kg. Treatment caused increased fetal mortality (100 mg/kg), decreased fetal weight (30 and 100 mg/kg), increased incidence of a skeletal abnormality (fused sternebrae at 30 and 100 mg/kg) and minor skeletal variations (100 mg/kg).

In a study in which rats were treated with oral doses of 3, 10, and 30 mg/kg/day (1, 3, and 10 times the MRHD on a  $\text{mg}/\text{m}^2$  basis) of aripiprazole perinatally and postnatally (from day 17 of gestation through day 21 postpartum), slight maternal toxicity

and slightly prolonged gestation were seen at 30 mg/kg. An increase in stillbirths, and decreases in pup weight (persisting into adulthood) and survival, were seen at this dose.

There are no adequate and well-controlled studies in pregnant women. It is not known whether aripiprazole can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Aripiprazole should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

## **Labor and Delivery**

The effect of aripiprazole on labor and delivery in humans is unknown.

## **Nursing Mothers**

Aripiprazole was excreted in milk of rats during lactation. It is not known whether aripiprazole or its metabolites are excreted in human milk. It is recommended that women receiving aripiprazole should not breast-feed.

## **Pediatric Use**

Safety and effectiveness in pediatric and adolescent patients have not been established.

## **Geriatric Use**

Of the 5592 patients treated with aripiprazole in premarketing clinical trials, 659 (12%) were  $\geq 65$  years old and 525 (9%) were  $\geq 75$  years old. The majority (91%) of the 659 patients were diagnosed with dementia of the Alzheimer's type.

Placebo-controlled studies of aripiprazole in schizophrenia did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. There was no effect of age on the pharmacokinetics of a single 15-mg dose of aripiprazole. Aripiprazole clearance was decreased by 20% in elderly subjects ( $\geq 65$  years) compared to younger adult subjects (18 to 64 years), but there was no detectable effect of age in the population pharmacokinetic analysis in schizophrenia patients.

Studies of elderly patients with psychosis associated with Alzheimer's disease have suggested that there may be a different tolerability profile in this population compared to younger patients with schizophrenia (see **PRECAUTIONS: Use in Patients**

with *Concomitant Illness*). The safety and efficacy of ABILIFY in the treatment of patients with psychosis associated with Alzheimer's disease has not been established. If the prescriber elects to treat such patients with ABILIFY, vigilance should be exercised.

## ADVERSE REACTIONS

Aripiprazole has been evaluated for safety in 5592 patients who participated in multiple-dose, premarketing trials in schizophrenia, bipolar mania, and dementia of the Alzheimer's type, and who had approximately 3639 patient-years of exposure. A total of 1887 aripiprazole-treated patients were treated for at least 180 days and 1251 aripiprazole-treated patients had at least 1 year of exposure.

The conditions and duration of treatment with aripiprazole included (in overlapping categories) double-blind, comparative and noncomparative open-label studies, inpatient and outpatient studies, fixed- and flexible-dose studies, and short- and longer-term exposure.

Adverse events during exposure were obtained by collecting volunteered adverse events, as well as results of physical examinations, vital signs, weights, laboratory analyses, and ECG. Adverse experiences were recorded by clinical investigators using terminology of their own choosing. In the tables and tabulations that follow, modified COSTART dictionary terminology has been used initially to classify reported adverse events into a smaller number of standardized event categories, in order to provide a meaningful estimate of the proportion of individuals experiencing adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. There was no attempt to use investigator causality assessments; ie, all reported events are included.

The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatment, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the adverse event incidence in the population studied.

## **Adverse Findings Observed in Short-Term, Placebo-Controlled Trials of Patients with Schizophrenia**

The following findings are based on a pool of five placebo-controlled trials (four 4-week and one 6-week) in which aripiprazole was administered in doses ranging from 2 to 30 mg/day.

### **Adverse Events Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials**

Overall, there was no difference in the incidence of discontinuation due to adverse events between aripiprazole-treated (7%) and placebo-treated (9%) patients. The types of adverse events that led to discontinuation were similar between the aripiprazole and placebo-treated patients.

### **Adverse Events Occurring at an Incidence of 2% or More Among Aripiprazole-Treated Patients and Greater than Placebo in Short-Term, Placebo-Controlled Trials**

Table 1 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during acute therapy (up to 6 weeks), including only those events that occurred in 2% or more of patients treated with aripiprazole (doses  $\geq 2$  mg/day) and for which the incidence in patients treated with aripiprazole was greater than the incidence in patients treated with placebo.

**Table 1: Treatment-Emergent Adverse Events in Short-Term, Placebo-Controlled Trials**

Body System Adverse Event	Percentage of Patients Reporting Event <sup>a</sup>	
	Aripiprazole (n=926)	Placebo (n=413)
<b>Body as a Whole</b>		
Headache	32	25
Asthenia	7	5
Fever	2	1
<b>Digestive System</b>		
Nausea	14	10
Vomiting	12	7
Constipation	10	8
<b>Nervous System</b>		
Anxiety	25	24
Insomnia	24	19
Lightheadedness	11	7
Somnolence	11	8
Akathisia	10	7
Tremor	3	2
<b>Respiratory System</b>		
Rhinitis	4	3
Coughing	3	2
<b>Skin and Appendages</b>		
Rash	6	5
<b>Special Senses</b>		
Blurred vision	3	1

<sup>a</sup> Events reported by at least 2% of patients treated with aripiprazole, except the following events, which had an incidence equal to or less than placebo: abdominal pain, accidental injury, back pain, dental pain, dyspepsia, diarrhea, dry mouth, myalgia, agitation, psychosis, extrapyramidal syndrome, hypertonia, pharyngitis, upper respiratory tract infection, dysmenorrhea, vaginitis.

An examination of population subgroups did not reveal any clear evidence of differential adverse event incidence on the basis of age, gender, or race.

## **Dose-Related Adverse Events**

Dose response relationships for the incidence of treatment-emergent adverse events were evaluated from four trials comparing various fixed doses (2, 10, 15, 20, and 30 mg/day) of aripiprazole to placebo. This analysis, stratified by study, indicated that the only adverse event to have a possible dose response relationship, and then most prominent only with 30 mg, was somnolence (placebo, 7.7%; 15 mg, 8.7%; 20 mg, 7.5%; 30 mg, 15.3%).

## **Extrapyramidal Symptoms**

In the short-term, placebo-controlled trials, the incidence of reported EPS for aripiprazole-treated patients was 6% vs. 6% for placebo. Objectively collected data from those trials on the Simpson Angus Rating Scale (for EPS), the Barnes Akathisia Scale (for akathisia), and the Assessments of Involuntary Movement Scales (for dyskinesias) also did not show a difference between aripiprazole and placebo, with the exception of the Barnes Akathisia Scale (aripiprazole, 0.08; placebo, -0.05).

Similarly, in a long-term (26-week) placebo-controlled trial, objectively collected data on the Simpson Angus Rating Scale (for EPS), the Barnes Akathisia Scale (for akathisia), and the Assessments of Involuntary Movement Scales (for dyskinesias) did not show a difference between aripiprazole and placebo.

## **Laboratory Test Abnormalities**

A between group comparison for 4- to 6-week placebo-controlled trials revealed no medically important differences between the aripiprazole and placebo groups in the proportions of patients experiencing potentially clinically significant changes in routine serum chemistry, hematology, or urinalysis parameters. Similarly, there were no aripiprazole/placebo differences in the incidence of discontinuations for changes in serum chemistry, hematology, or urinalysis.

In a long-term (26-week) placebo-controlled trial there were no medically important differences between the aripiprazole and placebo patients in the mean change from baseline in prolactin, fasting glucose, triglyceride, HDL, LDL, and total cholesterol measurements.

## Weight Gain

In short-term trials, there was a slight difference in mean weight gain between aripiprazole and placebo patients (+0.7 kg vs. -0.05 kg, respectively), and also a difference in the proportion of patients meeting a weight gain criterion of  $\geq 7\%$  of body weight [aripiprazole (8%) compared to placebo (3%)].

Table 2 provides the weight change results from a long-term (26-week) placebo-controlled study of aripiprazole, both mean change from baseline and proportions of patients meeting a weight gain criterion of  $\geq 7\%$  of body weight relative to baseline, categorized by BMI at baseline:

**Table 2: Weight Change Results Categorized by BMI at Baseline: Placebo-Controlled Study in Schizophrenia, Safety Sample**

	BMI <23		BMI 23-27		BMI >27	
	Placebo	Aripiprazole	Placebo	Aripiprazole	Placebo	Aripiprazole
Mean change from baseline (kg)	-0.5	-0.5	-0.6	-1.3	-1.5	-2.1
% with $\geq 7\%$ increase BW	3.7%	6.8%	4.2%	5.1%	4.1%	5.7%

Table 3 provides the weight change results from a long-term (52-week) study of aripiprazole, both mean change from baseline and proportions of patients meeting a weight gain criterion of  $\geq 7\%$  of body weight relative to baseline, categorized by BMI at baseline:

**Table 3: Weight Change Results Categorized by BMI at Baseline**

	BMI <23	BMI 23-27	BMI >27
Mean change from baseline (kg)	2.6	1.4	-1.2
% with $\geq 7\%$ increase BW	30%	19%	8%

## ECG Changes

Between group comparisons for pooled, placebo-controlled trials revealed no significant differences between aripiprazole and placebo in the proportion of patients experiencing potentially important changes in ECG parameters; in fact, within the dose range of 10 to 30 mg/day, aripiprazole tended to slightly shorten the QTc interval. Aripiprazole was

associated with a median increase in heart rate of 4 beats per minute compared to a 1 beat per minute increase among placebo patients.

## **Additional Findings Observed in Clinical Trials**

### **Adverse Events in a Long-Term, Double-Blind, Placebo-Controlled Trial**

The adverse events reported in a 26-week, double-blind trial comparing ABILIFY and placebo were generally consistent with those reported in the short-term, placebo-controlled trials, except for a higher incidence of tremor [9% (13/153) for ABILIFY vs. 1% (2/153) for placebo]. In this study, the majority of the cases of tremor were of mild intensity (9/13 mild and 4/13 moderate), occurred early in therapy (9/13  $\leq$ 49 days) and were of limited duration (9/13  $\leq$ 10 days). Tremor infrequently led to discontinuation (<1%) of ABILIFY. In addition, in a long-term (52-week) active controlled study, the incidence of tremor for ABILIFY was 4% (34/859).

### **Other Adverse Events Observed During the Premarketing Evaluation of Aripiprazole**

Following is a list of modified COSTART terms that reflect treatment-emergent adverse events as defined in the introduction to the **ADVERSE REACTIONS** section reported by patients treated with aripiprazole at multiple doses  $\geq$ 2 mg/day during any phase of a trial within the database of 5592 patients. All reported events are included except those already listed in Table 1, or other parts of the **ADVERSE REACTIONS** section, those considered in the **WARNINGS** or **PRECAUTIONS**, those event terms which were so general as to be uninformative, events reported with an incidence of <0.05% and which did not have a substantial probability of being acutely life-threatening, events that are otherwise common as background events, and events considered unlikely to be drug related. It is important to emphasize that, although the events reported occurred during treatment with aripiprazole, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

*Body as a Whole: Frequent* - flu syndrome, peripheral edema, chest pain, neck pain, neck rigidity; *Infrequent* - pelvic pain, suicide attempt, face edema, malaise, photosensitivity, arm rigidity, jaw pain, chills, bloating, jaw tightness, enlarged abdomen, chest tightness; *Rare* - throat pain, back tightness, head heaviness, moniliasis, throat tightness, leg rigidity, neck tightness, Mendelson's syndrome, heat stroke.

*Cardiovascular System: Frequent* - hypertension, tachycardia, hypotension, bradycardia; *Infrequent* - palpitation, hemorrhage, myocardial infarction, prolonged QT interval, cardiac arrest, atrial fibrillation, heart failure, AV block, myocardial ischemia, phlebitis, deep vein thrombosis, angina pectoris, extrasystoles; *Rare* - vasovagal reaction, cardiomegaly, atrial flutter, thrombophlebitis.

*Digestive System: Frequent* - anorexia, nausea and vomiting; *Infrequent* - increased appetite, gastroenteritis, dysphagia, flatulence, gastritis, tooth caries, gingivitis, hemorrhoids, gastroesophageal reflux, gastrointestinal hemorrhage, periodontal abscess, tongue edema, fecal incontinence, colitis, rectal hemorrhage, stomatitis, mouth ulcer, cholecystitis, fecal impaction, oral moniliasis, cholelithiasis, eructation, intestinal obstruction, peptic ulcer; *Rare* - esophagitis, gum hemorrhage, glossitis, hematemesis, melena, duodenal ulcer, cheilitis, hepatitis, hepatomegaly, pancreatitis, intestinal perforation.

*Endocrine System: Infrequent* - hypothyroidism; *Rare* - goiter, hyperthyroidism.

*Hemic/Lymphatic System: Frequent* - ecchymosis, anemia; *Infrequent* - hypochromic anemia, leukopenia, leukocytosis, lymphadenopathy, thrombocytopenia; *Rare* - eosinophilia, thrombocythemia, macrocytic anemia.

*Metabolic and Nutritional Disorders: Frequent* - weight loss, creatine phosphokinase increased; *Infrequent* - dehydration, edema, hypercholesteremia, hyperglycemia, hypokalemia, diabetes mellitus, SGPT increased, hyperlipemia, hypoglycemia, thirst, BUN increased, hyponatremia, SGOT increased, alkaline phosphatase increased, iron deficiency anemia, creatinine increased, bilirubinemia, lactic dehydrogenase increased, obesity; *Rare* - hyperkalemia, gout, hypernatremia, cyanosis, hyperuricemia, hypoglycemic reaction.

*Musculoskeletal System: Frequent* - muscle cramp; *Infrequent* - arthralgia, bone pain, myasthenia, arthritis, arthrosis, muscle weakness, spasm, bursitis; *Rare* - rhabdomyolysis, tendonitis, tenosynovitis, rheumatoid arthritis, myopathy.

*Nervous System: Frequent* - depression, nervousness, increased salivation, hostility, suicidal thought, manic reaction, abnormal gait, confusion, cogwheel rigidity; *Infrequent* - dystonia, twitch, impaired concentration, paresthesia, vasodilation, hypesthesia, extremity tremor, impotence, bradykinesia, decreased libido, panic attack, apathy, dyskinesia, hypersomnia, vertigo, dysarthria, tardive dyskinesia, ataxia, impaired memory, stupor, increased libido, amnesia, cerebrovascular accident, hyperactivity, depersonalization, hypokinesia, restless leg, myoclonus, dysphoria, neuropathy, increased reflexes, slowed thinking, hyperkinesia, hyperesthesia, hypotonia, oculogyric crisis; *Rare* - delirium, euphoria, buccoglossal syndrome, akinesia, blunted affect, decreased consciousness, incoordination, cerebral ischemia, decreased reflexes, obsessive thought, intracranial hemorrhage.

*Respiratory System: Frequent* - dyspnea, pneumonia; *Infrequent* - asthma, epistaxis, hiccup, laryngitis; *Rare* - hemoptysis, aspiration pneumonia, increased sputum, dry nasal passages, pulmonary edema, pulmonary embolism, hypoxia, respiratory failure, apnea.

*Skin and Appendages: Frequent* - dry skin, pruritus, sweating, skin ulcer; *Infrequent* - acne, vesiculobullous rash, eczema, alopecia, psoriasis, seborrhea; *Rare* - maculopapular rash, exfoliative dermatitis, urticaria.

*Special Senses: Frequent* - conjunctivitis, ear pain; *Infrequent* - dry eye, eye pain, tinnitus, otitis media, cataract, altered taste, blepharitis; *Rare* - increased lacrimation, frequent blinking, otitis externa, amblyopia, deafness, diplopia, eye hemorrhage, photophobia.

*Urogenital System: Frequent* - urinary incontinence; *Infrequent* - cystitis, urinary frequency, leukorrhea, urinary retention, hematuria, dysuria, amenorrhea, abnormal ejaculation, vaginal hemorrhage, vaginal moniliasis, kidney failure, uterus hemorrhage, menorrhagia, albuminuria, kidney calculus, nocturia, polyuria, urinary urgency; *Rare* - breast pain, cervicitis, female lactation, anorgasm, urinary burning, glycosuria, gynecomastia, urolithiasis, priapism.

## **DRUG ABUSE AND DEPENDENCE**

### **Controlled Substance**

ABILIFY (aripiprazole) is not a controlled substance.

## Abuse and Dependence

Aripiprazole has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. In physical dependence studies in monkeys, withdrawal symptoms were observed upon abrupt cessation of dosing. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of ABILIFY misuse or abuse (eg, development of tolerance, increases in dose, drug-seeking behavior).

## OVERDOSAGE

### Human Experience

In premarketing clinical studies, involving more than 5500 patients, accidental or intentional acute overdosage of aripiprazole was identified in seven patients. In the two patients taking the largest identified amount, 180 mg, the only symptoms reported were somnolence and vomiting in one of the two patients. In the patients who were evaluated in hospital settings, including the two patients taking 180 mg, there were no observations indicating an adverse change in vital signs, laboratory assessments, or ECG. An uneventful, accidental overdose (15 mg) occurred in a non-patient, an 18-month-old child, with concomitant ingestion of ATIVAN<sup>®</sup> (2 mg).

### Management of Overdosage

No specific information is available on the treatment of overdose with aripiprazole. An electrocardiogram should be obtained in case of overdosage and, if QTc interval prolongation is present, cardiac monitoring should be instituted. Otherwise, management of overdose should concentrate on supportive therapy, maintaining an adequate airway, oxygenation and ventilation, and management of symptoms. Close medical supervision and monitoring should continue until the patient recovers.

*Charcoal:* In the event of an overdose of ABILIFY, an early charcoal administration may be useful in partially preventing the absorption of aripiprazole.

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Administration of 50 g of activated charcoal, one hour after a single 15-mg oral dose of aripiprazole, decreased the mean AUC and C<sub>max</sub> of aripiprazole by 50%.

*Hemodialysis:* Although there is no information on the effect of hemodialysis in treating an overdose with aripiprazole, hemodialysis is unlikely to be useful in overdose management since aripiprazole is highly bound to plasma proteins.

## **DOSAGE AND ADMINISTRATION**

### **Usual Dose**

The recommended starting and target dose for ABILIFY is 10 or 15 mg/day administered on a once-a-day schedule without regard to meals. ABILIFY has been systematically evaluated and shown to be effective in a dose range of 10 to 30 mg/day, however, doses higher than 10 or 15 mg/day, the lowest doses in these trials, were not more effective than 10 or 15 mg/day. Dosage increases should not be made before 2 weeks, the time needed to achieve steady state.

### **Dosage in Special Populations**

Dosage adjustments are not routinely indicated on the basis of age, gender, race, or renal or hepatic impairment status (see **CLINICAL PHARMACOLOGY: Special Populations**).

*Dosage adjustment for patients taking aripiprazole concomitantly with potential CYP3A4 inhibitors:* When concomitant administration of ketoconazole with aripiprazole occurs, aripiprazole dose should be reduced to one-half of the usual dose. When the CYP3A4 inhibitor is withdrawn from the combination therapy, aripiprazole dose should then be increased.

*Dosage adjustment for patients taking aripiprazole concomitantly with potential CYP2D6 inhibitors:* When concomitant administration of potential CYP2D6 inhibitors such as quinidine, fluoxetine, or paroxetine with aripiprazole occurs, aripiprazole dose should be reduced at least to one-half of its normal dose. When the CYP2D6 inhibitor is withdrawn from the combination therapy, aripiprazole dose should then be increased.

*Dosage adjustment for patients taking potential CYP3A4 inducers:* When a potential CYP3A4 inducer such as carbamazepine is added to aripiprazole therapy, the aripiprazole dose should be doubled (to 20 or 30 mg). Additional dose increases should

be based on clinical evaluation. When carbamazepine is withdrawn from the combination therapy, the aripiprazole dose should be reduced to 10 to 15 mg.

## **Maintenance Therapy**

While there is no body of evidence available to answer the question of how long a patient treated with aripiprazole should remain on it, systematic evaluation of patients with schizophrenia who had been symptomatically stable on other antipsychotic medications for periods of 3 months or longer, were discontinued from those medications, and were then administered ABILIFY 15 mg/day and observed for relapse during a period of up to 26 weeks demonstrated a benefit of such maintenance treatment (see **CLINICAL PHARMACOLOGY: Clinical Studies**). Patients should be periodically reassessed to determine the need for maintenance treatment.

## **Switching from Other Antipsychotics**

There are no systematically collected data to specifically address switching patients with schizophrenia from other antipsychotics to ABILIFY or concerning concomitant administration with other antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some patients with schizophrenia, more gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized.

## **ANIMAL TOXICOLOGY**

Aripiprazole produced retinal degeneration in albino rats in a 26-week chronic toxicity study at a dose of 60 mg/kg and in a 2-year carcinogenicity study at doses of 40 and 60 mg/kg. The 40- and 60-mg/kg doses are 13 and 19 times the maximum recommended human dose (MRHD) based on mg/m<sup>2</sup> and 7 to 14 times human exposure at MRHD based on AUC. Evaluation of the retinas of albino mice and of monkeys did not reveal evidence of retinal degeneration. Additional studies to further evaluate the mechanism have not been performed. The relevance of this finding to human risk is unknown.

## **HOW SUPPLIED**

ABILIFY™ (aripiprazole) Tablets are available in the following strengths and packages.

The 5-mg ABILIFY tablets are blue, modified rectangular tablets, debossed on one side with “A-007” and “5”.

Bottles of 30 NDC 59148-007-13

Blister of 100 NDC 59148-007-35

The 10-mg ABILIFY tablets are pink, modified rectangular tablets, debossed on one side with “A-008” and “10”.

Bottles of 30 NDC 59148-008-13

Blister of 100 NDC 59148-008-35

The 15-mg ABILIFY tablets are yellow, round tablets, debossed on one side with “A-009” and “15”.

Bottles of 30 NDC 59148-009-13

Blister of 100 NDC 59148-009-35

The 20-mg ABILIFY tablets are white, round tablets, debossed on one side with “A-010” and “20”.

Bottles of 30 NDC 59148-010-13

Blister of 100 NDC 59148-010-35

The 30-mg ABILIFY tablets are pink, round tablets, debossed on one side with “A-011” and “30”.

Bottles of 30 NDC 59148-011-13

Blister of 100 NDC 59148-011-35

## **Storage**

Store at 25° C (77° F); excursions permitted to 15-30° C (59-86° F) [see USP Controlled Room Temperature].

Marketed by Otsuka America Pharmaceutical, Inc, Rockville, MD 20850 USA and  
Bristol-Myers Squibb Company, Princeton, NJ 08543 USA

Manufactured and Distributed by Bristol-Myers Squibb Company, Princeton, NJ 08543  
USA

U.S. Patent Nos. 4,734,416 and 5,006,528



**Bristol-Myers Squibb Company**



**Otsuka America Pharmaceutical, Inc.**

xxxxxxx

Revised xxxxxxx xxx

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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 21-436/S-001**

**MEDICAL REVIEW**

## REVIEW AND EVALUATION OF CLINICAL DATA

### Application Information

NDA#: 21-436/<sup>5E1</sup>~~SE6~~-001  
Sponsor: Otsuka/Bristol-Myers Squibb  
Due Date: October 3, 2003

### Drug Name:

Generic Name: Aripiprazole Tablets  
Trade Name: Abilify

### Drug Categorization:

Pharmacological Class: D<sub>2</sub> Receptor Partial Agonist  
Proposed Indication: Schizophrenia (Long-Term TX)  
Dosage Forms: 10mg, 15mg, 30mg tablets  
Route: Oral

### Review Information

Clinical Reviewers: Gregory M. Dubitsky, M.D.  
Completion Date: July 10, 2003

**NDA 21-436/SE6-001**  
**ARIPIPRAZOLE TABLETS FOR THE LONG-TERM**  
**TREATMENT OF SCHIZOPHRENIA**  
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## **EXECUTIVE SUMMARY**

### **I. Recommendations**

#### **A. Recommendation on Approvability**

Assuming that the sponsor agrees to the minor labeling change described in section X., it is recommended that this supplement be approved.

#### **B. Recommendation for Phase 4 Studies**

There are no recommendations for Phase 4 studies at this time.

### **II. Summary of Clinical Findings**

#### **A. Brief Overview of the Clinical Program**

This supplement provides data to support the longer-term efficacy of aripiprazole tablets (Abilify) in the treatment of adults with schizophrenia. These data derive from a single study, CN138-047. This was a 26-week, multicenter, randomized, double-blind, placebo-controlled study of a fixed dose of aripiprazole 15 mg/day in stabilized patients with chronic schizophrenia.

#### **B. Efficacy**

Study CN138-047 demonstrated the efficacy of aripiprazole 15 mg/day versus placebo in significantly reducing the risk of relapse in stabilized patients with chronic schizophrenia over a 26 week treatment period.

#### **C. Safety**

There were no safety findings from study CN138-047 which suggested previously unknown, important hazards associated with the longer-term use of aripiprazole in the treatment of schizophrenia.

#### **D. Dosing**

Study CN138-047 utilized a fixed 15 mg/day dose of aripiprazole. This is a currently recommended initial and target dose for the treatment of patients with acute schizophrenia.

#### **E. Special Populations**

This supplement provided no new data regarding the use of aripiprazole in special populations.

### **CLINICAL REVIEW**

#### **I. Introduction**

##### **A. Background**

Aripiprazole, a quinolinone derivative, is a novel psychotropic agent that exhibits partial agonism at D<sub>2</sub> receptors and 5-HT<sub>1A</sub> receptors and antagonism at 5-HT<sub>2A</sub> receptors. Aripiprazole tablets were approved as Abilify for the treatment of schizophrenia in adults on 11-15-02. Prior to approval, the sponsor made a post-approval commitment to submit the results of study CN138-047 to address the longer-term efficacy of aripiprazole in this indication. This supplement contains the results of this trial.

##### **B. Safety Findings with Aripiprazole**

In patients with schizophrenia, aripiprazole is not known to possess any remarkable toxicities.

##### **C. Administrative History**

As noted above, this supplement is intended to fulfill a post-approval commitment described in the approval letter for aripiprazole tablets in schizophrenia.

This supplement was submitted to the Agency on 12-3-02 and was received on 12-4-02. A Refuse-to-File meeting was held on 1-28-03 and the application was deemed fileable. The User Fee Due Date is 10-3-03.

#### **D. Proposed Instructions for Use**

No changes to the currently labeled dosing regimen are proposed: the recommended starting dose and target dose is 10 or 15 mg/day given once daily with or without food.

#### **E. Foreign Marketing**

Abilify has been approved for marketing in Mexico (July 2002), Brazil (November 2002), and Puerto Rico (November 2002). Applications for aripiprazole are under review in the European Union, Australia, Switzerland, [ ] [ ]. No adverse actions have been taken against any marketing application for aripiprazole.

### **II. Clinically Relevant Findings from Consultant Reviews**

#### **A. Statistical Review and Evaluation**

The Statistical Review and Evaluation is being completed by Peiling Yang, Ph.D., of the Division of Biometrics I (HFD-710). Her final review is pending at this time. This application has been discussed with Dr. Yang and her draft review was examined by the undersigned. There is general concurrence between us with respect to the overall interpretation of the efficacy results presented in this supplement.

#### **B. DSI Clinical Site Inspections**

Two centers were inspected by the Division of Scientific Investigations (DSI): center 007 (Mary Ann Knesevich, M.D., of the St. Paul Medical Center, Dallas, TX) and center 010 (David A. Sack, M.D., of the Institute for Psychopharmacology Research, Cerritos, CA). These centers were chosen based on relatively large numbers of enrolled patients (17 patients at center 007 and 19 patients at center 010). The findings of these inspections are conveyed in a Clinical Inspection Summary from Ni A. Khin, M.D., DSI Medical Officer, dated 4-9-03.

At center 007, records for all 17 subjects were audited. There were no major findings and this center was classified NAI (no deviation from regulations, data acceptable).

At center 010, records for 8 of the 19 subjects were audited. There were several findings at center 010:

- the investigator did not complete CGI Improvement ratings for 6 subjects at various time points specified in the report.
- the investigator did not immediately report information to the sponsor regarding 2 patients who had serious adverse experiences.
- the investigator failed to report information to the IRB regarding one patient who had a serious adverse event.

This center was classified VAI (minor deviation from regulations, data acceptable).

### **III. Human Pharmacokinetics and Pharmacodynamics**

#### **A. Pharmacodynamics**

No new pharmacodynamic data are presented in this sNDA.

#### **B. Pharmacokinetics**

No new pharmacokinetic data are presented in this sNDA.

### **IV. Description of Clinical Data Sources**

#### **A. Primary Development Program**

A total of 310 patients were randomized to treatment in study CN138-047 (155 each to aripiprazole and placebo). The Safety Sample was defined as all randomized patients who took at least one dose of double-blind study medication and comprised a total of 306 patients, 153 in each treatment group.

In this trial, the two treatment groups were comparable in terms of mean age and age range, gender, and race. Demographic characteristics are summarized in **Appendix IV-1**. Only 7 patients who were 65 years of age or older received aripiprazole in study CN138-047.

Patients in this trial who were randomized to aripiprazole received a fixed dose of 15 mg/day for up to 26 weeks. The number of patients receiving study medication by time interval is displayed in **Appendix IV-2**. Seventy-one aripiprazole patients completed 26 weeks of double-blind treatment.

## **B. Literature Search**

Literature searches were conducted by Yuri Takagaki, a licensed database searcher from Otsuka Pharmaceutical Company-Japan, and by Julia Chuang, Senior Information Scientist II from Bristol-Myers Squibb. The latter search covered the time period from January 1, 2002, through February 3, 2003. Search terms and literature databases are described in the sponsor's 3-28-03 submission.

Sixty-six articles were identified and reviewed in detail. Warrants are provided in the 3-28-03 submission from both Joy Parris, M.D., of Otsuka Maryland Research Institute, Inc., and Margaretta Nyilas, M.D., of Bristol-Myers Squibb, that this literature contains no findings that would adversely affect the conclusions about the safety of aripiprazole contained in this supplement.

## **V. Clinical Review Methods**

### **A. Items Utilized in the Review**

The items utilized in this review are listed in **Appendix V-1**.

### **B. Specific Methods Used to Evaluate Data Quality**

The Division of Scientific Investigations (DSI) performed on-site inspections at two centers (007 and 010) to audit the quality of records from this trial (see section II.B. for details). Although there were a number of findings noted at center 010, the data from both centers were deemed to be clinically acceptable.

Also, the consistency of adverse event documentation between Case Report Forms, Narrative Summaries, and the adverse event data listing (AETXT terms) was audited by the undersigned. This audit was conducted on a randomly selected sample of 4 of the 35 patients in study CN138-047 who experienced a serious adverse event or who dropped out due to an adverse event.<sup>1</sup> No major discrepancies across these three data sources was identified for these four patients.

---

<sup>1</sup> The audited patients were 138047-7-122, 138047-7-123, 138047-5-64, and 138047-48-85.

Additionally, the coding of investigator adverse event terms (verbatim terms) to modified COSTART preferred terms was audited by the undersigned. This audit was conducted by comparing AETXT terms (event terms from the CRF's) to PTERM terms (modified COSTART dictionary terms) in the AE data listing FDA\_QADR.xpt. No major coding errors or irregularities were noted in this audit.

**C. Adherence to Accepted Ethical Standards**

The sponsor asserts that study CN138-047 was conducted in compliance with 21 CFR Parts 50 and 56 at U.S. centers, ICH/GCP principles at European centers, and the Declaration of Helsinki.

**D. Evaluation of Financial Disclosure**

As of 11-8-02, the sponsor had received financial disclosure statements from 36/36 investigators and 152/154 subinvestigators who took part in study CN138-047. No individual had disclosable information. The sponsor had utilized due diligence to obtain statements from the remaining two subinvestigators but had been unsuccessful.

**VI. Review of Efficacy**

**A. Overview of Studies Pertinent to Efficacy**

Data to support the longer-term efficacy of aripiprazole in adult patients with schizophrenia derives solely from study CN138-047.

**B. Study CN138-047**

Investigators/Study Centers

There were 31 centers in this study: 9 U.S. centers and 22 centers in Europe. The principal investigators are listed in **Appendix VI-1**. None of the principal investigators was listed by the Agency as disqualified or totally restricted as of 6-28-03.

Center #48 was discovered by the sponsor's Contract Research Organization to be in violation of ICH/GCP guidelines. This center was closed as soon as the violation was detected. Data from this center were excluded from the efficacy analyses of this trial. The

decision to exclude these data was made prior to the database lock and unblinding.

### Objectives

The primary study objective was to compare the time from randomization to relapse between treatment with aripiprazole 15 mg/day and treatment with placebo over a 26 week period in stabilized patients with schizophrenia.

Secondary study objectives were to assess the efficacy, safety, and tolerability of aripiprazole relative to placebo in stabilized patients with schizophrenia.

### Patient Selection

The study population consisted of men and women, age 18 and older, with a diagnosis of schizophrenia by DSM-IV criteria. The illness had to be considered stable (with no improvement or worsening of symptoms within the past 3 months) and chronic (the diagnosis must have been made at least 2 years prior to the study with a need for continued treatment).<sup>2</sup> Additionally, the PANSS Total Score had to be at least 60 (1-7 scale) at baseline with a score of 4 (moderate) or less on the hostility or uncooperativeness items and the CGI Severity of Illness score had to be 4 (moderately ill) or less. Patients had to be receiving current treatment with a neuroleptic and have shown previous response to neuroleptics. Women of childbearing potential must have had a negative pregnancy test within 72 hours of starting medication, must have been using acceptable contraception, and must not have been lactating.

Important exclusion criteria were:

- currently in acute relapse.
- DSM-IV diagnosis of schizoaffective or bipolar disorder.
- met DSM-IV criteria for any significant substance use disorder within the past 3 months.
- unstable thyroid pathology within the past 3 months.
- history or evidence of a medical condition that would have placed the patient at undue risk of a significant

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<sup>2</sup> Illness stability over the previous 3 months was determined from an assessment of the recent psychiatric history by the investigator (please see the sponsor's 2-20-03 submission). This was not based on documentation of symptomatology during a lead-in period.

adverse experience or would have interfered with safety or efficacy assessments.

- clinically significant abnormality on laboratory tests, vital signs, or ECG.

### Study Design

This was a multicenter, randomized, double-blind, placebo-controlled study of two parallel treatment groups, placebo and fixed dose aripiprazole 15 mg/day. Inpatient hospitalization was recommended during the first two weeks after randomization. All patients were required to be closely monitored throughout the double-blind treatment phase in a setting such as an inpatient unit, a partial hospitalization program, a supervised group living home, or an outpatient day care program.

After a 3-14 day screening period, eligible patients were randomized in a 1:1 ratio to double-blind treatment with either placebo or aripiprazole 15mg. Doses were taken once daily at approximately the same time each day. There was no requirement regarding the time of day for dosing.

Efficacy measures comprised the CGI and PANSS, both of which were rated at screening and baseline. After baseline, the PANSS was rated at the end of weeks 3, 6, 10, 18, and 26 and the CGI was rated at the end of weeks 1, 2, 3, 4, 6, 8, 10, 14, 18, 22, and 26. However, patients were clinically supervised on a daily basis to assess for possible worsening of symptoms and the need for an unscheduled visit. Patients were immediately withdrawn if a relapse occurred, a relapse being defined as one or more of the following:

- CGI Improvement score  $\geq 5$  (minimally worse) or
- PANSS hostility or uncooperativeness item score  $\geq 5$  (moderately severe) on 2 successive days or
- $\geq 20\%$  increase in the PANSS total score.

The duration of treatment was to be at least 26 weeks for patients randomized in the initial 2 month accrual period for the trial. Patients randomized after the 2 month accrual period were to be treated for at least 18 weeks. After 86 relapse events had occurred, patients who completed 26 weeks of treatment or who discontinued due to lack of efficacy could enter an 52 week open-label

extension phase.<sup>3</sup> Since the target of 86 relapse events was reached before any patient completed 26 weeks of double-blind treatment, only 26 weeks of treatment was required.

### Analysis

The primary efficacy variable was the time from randomization to relapse, defined as the date of relapse minus the date of first dosing plus one day.<sup>4</sup> Survival curves based on the above definition of relapse were estimated using Kaplan-Meier methodology and a log-rank test was used to compare survival distributions between the two treatment groups. Patients who did not relapse were censored on the later of the date of their last efficacy evaluation or the date of their last dose of study medication, including those who discontinued early for reasons other than relapse. This analysis was performed on the Efficacy Sample, i.e., all patients who were randomized, took at least one dose of study medication during the double-blind treatment phase, and had at least one post-randomization efficacy evaluation.<sup>5</sup>

Secondary efficacy measures included the mean change from randomization to week 6 on the PANSS total score, PANSS Negative Subscale, PANSS Positive Subscale, and CGI severity score. These variables were analyzed using ANCOVA with the randomization score as covariate. These analyses were performed on the Efficacy Sample.

### Baseline Demographics

Baseline demographic characteristics of the randomized sample are displayed by treatment group in **Appendix IV-1**. The aripiprazole and placebo groups were comparable in terms of mean age, age range, gender, and race.

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<sup>3</sup> According to the original protocol, a total of 86 events would be required to yield 90% power to detect a 23% difference between treatment groups in the percentage of patients relapsing. It was expected that the 6 month relapse rates for aripiprazole and placebo would be 32% and 55%, respectively.

<sup>4</sup> As noted by the statistical reviewer, Dr. Yang, the sponsor calls this "time from randomization to relapse" even though it is computed as the time from first dose to relapse, including the day of first dose and the day of relapse.

<sup>5</sup> The patient sample for the primary efficacy analysis was changed from the Safety Sample to the Efficacy Sample in an Administrative Letter dated 8-16-01.

The groups were also similar in terms of the mean age at the time of first diagnosis of schizophrenia.

### Baseline Severity of Illness

The aripiprazole and placebo groups were comparable in terms of baseline mean measures of illness severity:

	<u>Aripiprazole</u>	<u>Placebo</u>
PANSS total score	81.2	82.3
PANSS Negative Subscale	23.6	23.8
PANSS Positive Subscale	16.9	16.8
CGI Severity of Illness	3.5	3.5

An identical percentage of patients in each group (45.8%) were on full inpatient status at randomization.

The mean duration of stable symptoms of schizophrenia was slightly less in the aripiprazole group compared to placebo (12.3 vs. 16.3 months). No patient had less than 3 months of symptom stability.

### Patient Disposition

A total of 372 patients were enrolled and, of these, 72 failed screening criteria. However, 10 of these failures were randomized in error: 5 were randomized to aripiprazole and 5 to placebo.<sup>6</sup> Thus, a total of 310 patients were randomized, 155 to aripiprazole and 155 to placebo.

Amendment #3 to the study protocol indicated that 250 patients would be enrolled, with the expectation that 194 patients would be randomized. However, due to very rapid accrual, 310 patients were randomized within the first 2 months of the study. Since this increased sample size was not based on any results from the trial, it is unlikely that this increase introduced any bias although it certainly increased the statistical power to detect a difference between the two treatment groups.

Of the 310 randomized patients, 4 patients (2 randomized to aripiprazole and 2 to placebo) were excluded from the Safety Sample because they did not take any study medication. Thus, the Safety Sample comprised 306

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<sup>6</sup> Six of these 10 patients were from center #48 which was closed due to ICH/GCP violations.

patients, 153 in the aripiprazole group and 153 in the placebo group.

Finally, of these, an additional 9 patients were excluded from the Efficacy Sample. Thus, the Efficacy Sample comprised 297 patients, 148 in the aripiprazole group and 149 in the placebo group.

Patient disposition is summarized in **Appendix VI-2** for all randomized patients. In the aripiprazole group, 54% of the randomized sample dropped out of double-blind treatment compared to 71% of placebo patients. The predominant reason for dropout in both groups was lack of efficacy (27% of aripiprazole and 49% of placebo patients).

The numbers of patients receiving study medication by treatment group and time interval is displayed in **Appendix IV-2**.

#### Concomitant Medications

All psychotropic medications, except those prescribed by the protocol, were prohibited during double-blind treatment. Dose tapering of prohibited medications could be done during the screening phase. There was a minimum washout period of 3 days prior to baseline for neuroleptics and other psychotropics.

A summary of concomitant CNS medication usage is provided in **Appendix VI-3**. Similar proportions of aripiprazole and placebo patients used various classes of these agents. Concomitant antipsychotic drugs were taken by 3.3% (5/153) of aripiprazole and 2.0% (3/153) of placebo patients.

#### Efficacy Results

The primary efficacy measure was the time to relapse, as defined above. Kaplan-Meier survival curves were estimated for the aripiprazole and placebo patients in the Efficacy Sample and curves were compared using the log-rank test.

At week 2, the proportions of relapses were comparable between the two groups but, from week 4 onward, there were more relapses in the placebo group versus the aripiprazole group. Kaplan-Meier estimates of the probability of survival (i.e., not experiencing relapse) prior to week 26 were 39% for placebo and 63% for aripiprazole. These data

are summarized in **Appendix VI-4**. The survival curves are displayed in **Appendix VI-5**.

The log-rank test for equality of the survival curves indicated that the estimated probability of relapse over time was significantly greater in the placebo group compared to the aripiprazole group (p-value <0.001). Since less than 50% of the aripiprazole patients experienced relapse, the median time to relapse was not estimated. The aripiprazole:placebo hazard ratio for relapse was 0.503 (95% CI 0.354, 0.714).

Dr. Yang, the statistical reviewer, noted the following concerns in the sponsor's primary efficacy analysis:

- although the primary study objective was to assess the time from randomization to relapse, the time to relapse was actually computed from the date of first dosing to relapse. She identified 10 patients, 5 in each treatment group, where the date of randomization and the date of first dosing differed by more than 2 days. In her re-analysis, Dr. Yang computed and utilized the time from randomization to relapse.
- the date of relapse was defined as the earliest of the dates on which patients met at least one of the criteria for relapse. Dr. Yang identified some patients for whom the relapse date, by this definition, was different from the date indicated by the sponsor. This appeared to be due to some recording errors in the sponsor's database and was corrected in her re-analysis.
- the sponsor excluded from the Efficacy Sample 6 patients (from center 48) who were randomized but who did not meet inclusion/exclusion criteria. Dr. Yang asserts that these patients should have been included in the Efficacy Sample, as defined above. In her calculations, the Efficacy Sample comprised a total of 303 patients (151 randomized to aripiprazole and 152 to placebo).

Dr. Yang proceeded to repeat the primary efficacy analysis to adjust for the above concerns. Survival curves were re-estimated using Kaplan-Meier methodology and the curves were compared using the log-rank test, which yielded a p-value less than 0.001. The aripiprazole:placebo hazard ratio for relapse was 0.537 (95% CI 0.385, 0.748). The probability of survival at week 26 was estimated to be 35.7% for placebo and 58.9% for aripiprazole.

Thus, overall, Dr. Yang's analysis was consistent with the findings derived from the sponsor's analysis.

Dr. Yang also examined the reason(s) for relapse among the 57 aripiprazole and 92 placebo patients who relapsed in her analysis. The most common criteria by which patients were determined to have relapsed were 1) CGI improvement score  $\geq 5$  alone (53% of all relapse patients) and 2) simultaneous CGI improvement score  $\geq 5$  AND  $\geq 20\%$  increase in the PANSS total score (29% of all relapse patients).

According to the sponsor's a priori criteria for relapse, patients who experienced a score of  $\geq 5$  on the PANSS Hostility or Uncooperativeness items on 2 successive days were considered as relapsing. However, Dr. Yang observed that for patients who had a score of 5 or higher on either of these items on a given day, there was no recorded score for the following day. Nonetheless, the sponsor considered these patients as relapsing on the first day of such a score without meeting the formal criteria. She further observed that most of these patients met the PANSS total score criterion or the CGI criterion on these days and, thus, can legitimately be considered as relapsing. Since only two patients in each group were found to have relapsed solely on the basis of PANSS scores  $\geq 5$  on the Hostility or Uncooperativeness items, she does not feel that this issue significantly impacted on the overall study results. I concur.

Data regarding secondary efficacy measures are not relevant to the sponsor's claim and are not discussed in this review.

### Conclusions

The design of this study deviated from that typically utilized to provide evidence of longer-term efficacy. Typically, patients are treated on an open-label basis with the drug of interest for a number of weeks and those who respond, by some prespecified criteria, are randomized to drug or placebo and treated under double-blind conditions for 6-12 months.

In study CN138-047, eligible patients may have received treatment with any neuroleptic medication before study entry. Also, they had to be clinically stable by history over the preceding 3 months. Stability was not documented

during a lead-in period during which psychotic symptoms were rated with a validated instrument. Thus, this entry criterion is "softer" than that usually employed.

The potential consequences of these design features are that patients who were stable on their pre-study medication may have destabilized upon switching to aripiprazole. Also, some patients may have entered the study without being truly stable over the last 3 months by virtue of the "softer" entry criterion and, likewise, may have destabilized early in the trial. However, it seems most likely that these consequences would have mitigated against demonstrating a significant difference between aripiprazole and placebo and led to a negative study. Since the results of this trial were clearly positive, this feature of the study design is not a major concern to me.

Study CN138-047 demonstrated that aripiprazole 15 mg/day, relative to placebo, was efficacious in increasing the time to relapse in stabilized patients with chronic schizophrenia over 26 weeks of treatment.

## C. Summary of Data Pertinent to Important Clinical Issues

### 1. Predictors of Response

The sponsor examined time from randomization to relapse by various demographic and severity subgroups: gender (male vs. female), age group (18-50 years vs. >50 years), race (Caucasian vs. non-Caucasian), and baseline illness severity (defined by the median PANSS total score at baseline: <81 vs. ≥81). The results of these analyses are summarized in **Appendix VI-6**.<sup>7</sup>

Aripiprazole showed a statistically superior effect in increasing the time to relapse compared to placebo in each subgroup except two:

- in the elderly subgroup (patients over the age of 50 years), aripiprazole increased the time to relapse compared to placebo but not to a statistically significant degree (log-rank p-value =0.479). The aripiprazole:placebo hazard ratio favored drug but the 95% confidence interval for the hazard ratio did include 1.000 (HR=0.775, 95% CI= 0.382,

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<sup>7</sup> Full results were provided in a 2-20-03 submission. Please note that these analyses were performed on the sponsor-defined Efficacy Sample (N=297) and using time from first dose to relapse as the endpoint.

1.573). This finding may be attributable, in part, to the small subgroup sample size (35 aripiprazole and 36 placebo patients).

- in the non-Caucasian subgroup, aripiprazole was slightly worse than placebo (aripiprazole:placebo hazard ratio for relapse=1.638). However, the 95% confidence interval for the hazard ratio was quite large (0.510, 5.255), probably due to the small sample size (14 placebo and 15 aripiprazole patients), and the survival curves were not significantly different.

## **2. Size of Treatment Effect**

By Dr. Yang's analysis, the instantaneous risk for an aripiprazole patient to relapse was estimated to be 53.7% of that for a placebo patient given that the patient had not yet relapsed. Thus, aripiprazole appears to reduce the risk of relapse by about one-half relative to placebo. The Kaplan-Meier estimated probability of survival (not experiencing relapse) at week 26 was 35.7% for placebo patients and 58.9% for aripiprazole patients. The median time to relapse for the aripiprazole group was not estimated.

## **3. Choice of Dose**

Study CN138-047 employed a fixed dose of aripiprazole (15 mg/day). This is a currently recommended initial and target dose in the acute treatment of schizophrenia. It is not known whether higher doses would have reduced the risk of relapse even more or whether lower doses would have produced a comparable reduction in risk over the 26 week treatment period.

## **4. Duration of Treatment**

This trial demonstrated a reduced risk of relapse among patients treated with aripiprazole compared to placebo over a 26 week treatment period. A total of 116 patients, 71 treated with aripiprazole and 45 with placebo, completed the 26 week double-blind treatment period. This represents 45.8% of all patients randomized to aripiprazole and 29.0% of patients randomized to placebo.

## **D. Conclusions Regarding Efficacy**

Study CN138-047 demonstrated the efficacy of aripiprazole 15 mg/day versus placebo in significantly reducing the risk of relapse in stabilized patients with chronic schizophrenia over a 26 week treatment period. In elderly and non-Caucasian subgroups, this effect was not demonstrated, possibly due to the small size of these subgroups.

## **VII. Integrated Review of Safety**

### **A. Methodology of the Safety Review**

Safety data in this supplement derives solely from study CN138-047. A total of 306 patients (153 randomized to aripiprazole and 153 to placebo) comprised the Safety Sample in this trial.

This review examined the occurrence of deaths, non-fatal serious adverse experiences, and adverse events that led to premature discontinuation. Additionally, analyses of commonly occurring adverse events, laboratory tests, vital sign measurements, and 12-lead ECG tracings were also assessed.

The specific assessments and the timing of those safety measures in this study are presented in **Appendix VII-1**.

### **B. Safety Findings**

#### **1. Deaths**

One death (Patient 138047-7-117) was reported during the study. This was a 30 year old male in the aripiprazole treatment group who was involved in a fatal motor vehicle accident after his first dose of study medication. He was struck by two vehicles in the vicinity of a freeway. His death is not directly attributable to aripiprazole treatment.

#### **2. Serious Adverse Events**

A serious adverse event (SAE) was any untoward medical occurrence that met one of the following criteria:

- resulted in death.
- was life-threatening.
- required inpatient hospitalization or prolonged existing hospitalization.
- resulted in persistent or significant disability or incapacity.
- a cancer.
- a congenital anomaly or birth defect.
- resulted in an overdose
- resulted in the development of drug dependency or drug abuse.
- was an event that may have jeopardized the patient or may have required intervention to prevent one of the outcomes listed above.

Twenty patients had an SAE during the study or within 30 days after discontinuing study medication: 9 of these patients were in the placebo group and 11 in the aripiprazole group. All patients with an SAE are listed in **Appendix VII-2**. Narrative summaries for all aripiprazole patients who had an SAE were examined by the undersigned.

The most common SAE's were related to hospitalization for exacerbation of schizophrenic illness or for psychosocial reasons. One patient (138047-57-339) experienced a convulsion and loss of consciousness for one minute after receiving aripiprazole 15 mg/day for 7 days. Medication was discontinued. It was discovered after enrollment that this patient had a several year history of seizures prior to the study. An etiologic role for aripiprazole in this event is considered possible. Otherwise, no medically serious adverse events were felt to be attributable to aripiprazole treatment.

### **3. Dropouts due to Adverse Events**

Adverse events led to discontinuation of study medication in 11% (17/153) of aripiprazole patients and 8% (12/153) of placebo patients.

Adverse events that led to premature discontinuation are enumerated in **Appendix VII-3**. Narrative summaries for all aripiprazole patients who dropped out due to an adverse event were examined except for those due to schizophrenic reactions, which likely represented worsening of the primary illness. Except for the patient who experienced a seizure, which was described above, none of the reviewed

cases was felt to involve the occurrence of a medically serious event attributable to aripiprazole.

#### **4. Common Adverse Events**

##### **a. Categorization of Adverse Events**

Adverse events were classified by primary term according to a BMS Neuroscience-modified COSTART dictionary. As noted in section V.B. above, the coding of investigator terms to primary terms was audited by comparing AETXT terms (event terms from the CRF's) to PTERM terms (modified COSTART dictionary terms) in the AE data listing FDA\_QADR.xpt. No major coding errors or irregularities were found.

##### **b. Common, Drug-Related Adverse Events**

There was only one common, drug-related, treatment-emergent adverse experience: tremor (reported in 8.5% of aripiprazole- and 1.3% of placebo-treated patients).<sup>8</sup> The reporting rates for all treatment-emergent adverse experiences reported in at least 1% of aripiprazole-treated patients are displayed in **Appendix VII-4**.

##### **c. Extrapyramidal Symptoms**

The effects of aripiprazole on extrapyramidal symptoms were evaluated utilizing the Simpson Angus Scale (SAS), Abnormal Involuntary Movement Scale (AIMS), and the Barnes Akathisia Scale (BAS). Mean changes from baseline on these scales are summarized in study report Tables 12.5.1, 12.5.2, and 12.5.3, respectively.

Aripiprazole showed statistically greater improvement on the SAS compared to placebo. However, the difference between aripiprazole and placebo with respect to the mean change from baseline on the SAS was small and unlikely to be clinically important. There were no significant differences between aripiprazole and placebo on the AIMS or BAS.

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<sup>8</sup> Defined as an event reported in at least 5% of the aripiprazole patients at an incidence at least twice that in the placebo group.

#### d. Demographic Effects on Adverse Event Incidence

The sponsor explored the effect of demography on adverse event reporting rates for five specific adverse events: nausea, vomiting, akathisia, insomnia, and tremor.<sup>9</sup>

The aripiprazole:placebo odds ratio of each event being reported was computed for the following demographic subgroups:

Sex: Male vs. female.  
Age: 18-50 years vs. >50 years.  
Race: Caucasian vs. Non-Caucasian.

The Breslow-Day Chi-Square Test was then utilized to compare the odds ratios between subgroups for each variable. There was only one statistically significant finding at an alpha level of 0.10: the odds of insomnia was greater among older patients (odds ratio =2.46) than among younger patients (odds ratio =0.89) (p-value =0.072).<sup>10</sup>

#### 5. Laboratory Data

##### a. Potentially Clinically Significant Laboratory Changes

Criteria for identifying patients with potentially clinically significant (PCS) laboratory values are presented in Supplemental Tables S.6.3.4.3A and S6.3.4.3B of the report for Study CN138-047. The proportions of aripiprazole and placebo patients who met one of these criteria during treatment are provided in Table 12.6 and Supplemental Table S.12.6A of the study report.

There were no statistically significant increases in the aripiprazole group compared to placebo (alpha=0.10). However, the proportion of placebo patients meeting the PCS criterion for an elevated prolactin level (>ULN) was significantly greater than in the aripiprazole group (12.6% vs. 4.6%, p=0.02).

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<sup>9</sup> These events were suggested by the Agency because they were reported by at least 5% of the aripiprazole patients at an incidence greater than that in the placebo group.

<sup>10</sup> The results of this analysis are contained in a 2-20-03 submission from the sponsor.

There were 4 aripiprazole-treated patients who met PCS criteria for increased serum total bilirubin ( $\geq 2$  mg/dl).<sup>11</sup> None of these patients had associated increases in liver transaminases (ALT or AST) or jaundice. Bilirubin levels were all in the range of 2 to 2.9 mg/dl. There were no follow-up levels reported.

One aripiprazole patient had a PCS low relative neutrophil count (6%).<sup>12</sup> However, the absolute neutrophil count was 3,060/cmm and was unlikely to be clinically significant.

#### **b. Mean Change from Baseline in Laboratory Tests**

Mean changes from baseline in chemistry and hematology measures are summarized in Table 12.7 and Supplemental Table S.12.6C of the study report. Changes were compared between treatment groups by visual inspection.

The mean change from baseline in serum prolactin at week 26 (OC) showed substantial decreases for both aripiprazole and placebo, with larger decreases in the aripiprazole group: -24.15 ng/ml (N=61) versus -15.73 ng/ml (N=41). The placebo-adjusted difference (95% CI) was -7.80 ng/ml (-15.38, -0.23).

There was only one other remarkable difference between aripiprazole and placebo: patients on aripiprazole tended to experience increases in serum CPK relative to placebo-treated patients. At week 26 (OC), the mean change from baseline in CPK in the aripiprazole group was +88.29 U/L (N=70) compared to -10.68 U/L (N=44) in the placebo group. Median changes from baseline were much smaller but showed a similar trend (+7.00 versus -6.00 U/L, respectively). In the PCS abnormality analysis described above, the incidence of PCS CPK values was slightly greater for aripiprazole than for placebo (9.2% versus 7.2%). The clinical significance of this finding is unknown.

#### **c. Dropouts due to Laboratory Abnormalities**

There was only one dropout due to a laboratory test abnormality. Patient 138047-48-78 was a 50 year old male who treated with aripiprazole 15 mg/day for 10 days when he experienced an exacerbation of schizophrenia. Study

<sup>11</sup> Patients 138047-36-202, 138047-50-223, 138047-52-250, and 138047-61-208.

<sup>12</sup> Patient 138047-54-169.

medication was discontinued and he was discovered to have a CPK level of 2,288 U/L (199 U/L at screening). The only other symptom noted at that time was insomnia. No follow-up CPK values were provided. An explanation for the CPK elevation is unknown.

## **6. Vital Sign Data**

### **a. Potentially Clinically Significant Vital Sign Changes**

The criteria for identifying patients with PCS vital sign measurements are displayed in Supplemental Table S.6.3.4.4 of the study report for study CN138-047. The proportions of patients who met one of these criteria during double-blind treatment are displayed in Table 12.8.1 of the study report. Variables consisted of PCS increases or decreases in standing systolic and diastolic blood pressures, supine systolic and diastolic blood pressures, standing and supine heart rate, and weight change.

There were no statistically significant differences between aripiprazole and placebo in the proportions of patients with PCS vital sign measurements ( $\alpha=0.10$ ).

### **b. Mean Change from Baseline in Vital Sign Measures**

Mean changes from baseline in vital sign measurements are displayed in Supplemental Tables S.12.8.1B through S.12.8.1K of the study report. Included are mean changes in waist and hip circumference, body mass index, and body weight. Mean changes at week 26 (OC) were compared between aripiprazole and placebo by visual inspection.

The only remarkable difference between groups was for standing systolic blood pressure: the mean change from baseline in aripiprazole patients (N=70) was -3.81 mmHg versus -0.32 mmHg in placebo patients (N=44), a difference of about 3.5 mmHg. The median changes were -4.00 mmHg for aripiprazole and 0.00 for placebo.

### **c. Dropouts due to Vital Sign Abnormalities**

One patient (138047-48-141) dropped out of the study due to hypertension. This was a 73 year old male with no significant medical history treated with aripiprazole 15 mg/day. On day 14, he dropped out of the trial with blood pressure readings of 180/85 (supine) and 195/100

(standing); screening blood pressure readings were 125/70 (supine) and 130/70 (standing). He was treated with a number of medications, including captopril, indapamide, and enalapril. The event reportedly resolved on day 15 but no follow-up data were provided.

## 7. Electrocardiographic (ECG) Data

### a. Potentially Clinically Significant ECG Changes

Criteria for identifying PCS ECG measurements are listed in Supplemental Table S.6.3.4.5 in the study report for study CN138-047. QT intervals were corrected utilizing both Bazett's formula and the "FDA Neuropharmacology Division" formula ( $QTc = QT/RR^{0.37}$ ). The proportions of patients with PCS ECG abnormalities by treatment group are presented in Table 12.8.2B of the study report.

There were no statistically significant differences between aripiprazole and placebo in the proportions of patients with PCS ECG abnormalities ( $\alpha = 0.10$ ).

### b. Mean Change from Baseline in ECG Values

Mean changes from baseline for ECG parameters are tabulated in Table 5 of the sponsor's 2-20-03 submission to this supplement. Mean changes at week 26 (OC) were compared between the aripiprazole and placebo treatment arms by visual inspection.

Appreciable differences between aripiprazole (N=71) and placebo (N=43) were noted for QTc and heart rate. These data are summarized below.

<u>Mean Change (S.E.) from Baseline to Week 26 (OC)</u>		
<u>ECG Parameter</u>	<u>Placebo</u>	<u>Aripiprazole</u>
QTc Bazett (msec)	+1.26 (3.87)	-8.59 (3.06)
QTc Neuropharm (msec)	-0.84 (3.98)	-6.41 (2.75)
Heart Rate (bpm)	+2.53 (1.84)	-3.44 (1.86)

Based on these data, aripiprazole appeared to shorten the QTc and decrease heart rate relative to placebo. The clinical significance of these findings is unknown.

**c. Dropouts due to ECG Abnormalities**

One patient dropped out due to an ECG abnormality. Patient 138047-5-64 was a 40 year old male who had abnormal ECG readings during treatment with aripiprazole 15 mg/day. ECG's revealed non-specific ST-T wave changes, suggesting myocardial ischemia, and a left axis deviation on days 44, 57, and 77. The left axis deviation and "clinically irrelevant" ST-T wave changes had been observed at screening. He discontinued treatment on day 77. A subsequent myocardial perfusion study revealed no clinical evidence of myocardial ischemia.

**C. Adequacy of Patient Exposure and Safety Assessments**

The duration of patient exposure to aripiprazole from the original NDA safety database was adequate to meet ICH recommendations. In the non-Japanese Phase 2/3 studies from that database, 1513 patients received aripiprazole for at least 6 months and 902 patients received aripiprazole for at least one year. Safety data from study CN138-047 adds some additional exposure, with 71 patients having received aripiprazole at a therapeutic dose (15 mg/day) for at least 176 days (approximately 6 months) in this trial.

The safety assessments in study CN138-047 were sufficient to reasonably evaluate the longer-term safety of aripiprazole in this trial.

**D. Assessment of Data Quality and Completeness**

Safety data contained in this supplement generally appeared to be reasonably reliable and complete. The only notable deficiency was the apparent lack of follow-up on abnormal laboratory values and vital sign measurements observed in some patients. Given that this shortcoming was noted in a relatively small number of patients, it does not unduly impair the overall assessment of safety in this supplement.

More formal assessments of data quality and completeness were accomplished by an audit of Case Report Forms (CRF's), Narrative Summaries, and adverse event line listings; a 100% audit of adverse event coding to preferred terms, and DSI inspections of 2 centers (see sections II.B and V.B). These assessments did not reveal any findings which would significantly impact on the reliability of the submitted data.

## **E. Summary of Important Safety Findings**

There were no safety findings from study CN138-047 which suggested previously unknown, important hazards associated with the longer-term use of aripiprazole in the treatment of schizophrenia.

## **VIII. Dosing, Regimen, and Administration Issues**

The fixed dose of aripiprazole administered in study CN138-047 (15 mg/day) is a currently labeled initial and target dose for the treatment of acute schizophrenia. This study revealed no safety or efficacy concerns with the longer-term use of this dose in the treatment of stabilized patients with chronic schizophrenia.

## **IX. Use in Special Populations**

This supplement presented no specific data regarding the use of aripiprazole in special populations. Very few elderly patients received aripiprazole in study CN138-047 (7 patients age 65 or older).

## **X. Review of Proposed Labeling**

Following are the sponsor's revisions to labeling, as depicted in their draft labeling dated 11-26-02 submitted with this supplement:

### CLINICAL PHARMACOLOGY/Clinical Studies

A final paragraph is added to this section which summarizes study CN138-047. The proposed text is acceptable except for the fact that it states that the patients in this study were [ ] According to Table 8.4A of the study report, only 45.8% of the Randomized Sample (N=310) were on full inpatient status. Another 3.9% were in partial hospitalization programs and 34.8% were in outpatient day programs at study entry. Thus, this description should indicate that the study involved inpatients and outpatients. (This is the only change to the sponsor's proposed labeling felt to be warranted at this time.)

## INDICATIONS AND USAGE

The second paragraph, which states that the long-term efficacy of aripiprazole in the treatment of schizophrenia has not been established, is replaced by a paragraph indicating that Abilify was demonstrated to [ ] in study CN138-047. It [ ] advises physicians who elect to use Abilify for extended periods to periodically re-evaluate the long-term usefulness of the drug. This revision is acceptable.

## ADVERSE REACTIONS/Extrapyramidal Symptoms

The sponsor has added text indicating that, in study CN138-047, there were no differences between aripiprazole and placebo with respect to ratings on the Simpson Angus Scale, [ ] and the Abnormal Involuntary Movement Scale. This statement is supported by Tables 12.5.1, 12.5.3, and 12.5.2, respectively, in the study report and is acceptable.

## ADVERSE REACTIONS/Laboratory Test Abnormalities

The sponsor has added a statement that, based on study CN138-047, there were no medically important differences between aripiprazole and placebo in the mean change from baseline in prolactin, fasting glucose, triglyceride, LDL, and total cholesterol. This statement is consistent with data found in Supplemental Table S.12.6C of the study report and is acceptable.

## ADVERSE REACTIONS/Weight Gain

A table has been added to present the mean change from baseline (LOCF) in body weight as well as the proportion of patients with a weight gain of at least 7% of baseline weight from study CN138-047. Both analyses are presented by Body Mass Index category at baseline, consistent with a similar table currently in labeling. This table is supported by data from Supplemental Tables S.12.8.11 and S.12.8.1M in the study report and is acceptable.

## ADVERSE REACTIONS/Additional Findings Observed in Clinical Trials

A statement has been added to indicate that the adverse events reported in study CN138-047 were generally

consistent with those reported in short-term, placebo-controlled trials. A comparison between study CN138-047 and the pool of short-term studies in schizophrenia in the original NDA submission suggests that the types of adverse events reported were generally similar. Thus, I have no objection to this statement.

#### DOSAGE AND ADMINISTRATION/Maintenance Therapy

A statement has been added to indicate that a systematic evaluation of aripiprazole has shown that its efficacy in schizophrenia is maintained for periods up to 26 weeks at a dose of 15 mg/day. This language is acceptable.

#### **XI. Conclusions and Recommendations**

This supplement presents adequate data to show that aripiprazole 15 mg/day significantly [ ] of relapse among stabilized patients with chronic schizophrenia compared to placebo over a 6 month period. Previously reviewed safety data from longer-term exposure to aripiprazole, in conjunction with the safety data contained in this supplement, reveals no safety findings indicating a clinically important hazard associated with the longer-term administration of aripiprazole.

Assuming that the sponsor agrees to the labeling change recommended in section X. above, it is recommended that this supplement be approved.

Gregory M. Dubitsky, M.D.  
July 10, 2003

cc: NDA 21-436  
HFD-120/Division File  
HFD-120/GDubitsky  
/TLaughren  
/PAndreason  
/SHardeman

**SECTION XII**  
**APPENDICES**

**NDA DATA SOURCES**

**APPENDIX IV-1  
STUDY CN138-047  
DEMOGRAPHIC CHARACTERISTICS**

Variable		Placebo	Aripiprazole	Total
		N = 155	N = 155	N = 310
Age (years)	Mean	41.7	42.2	42.0
	Median	41.0	42.0	42.0
	Min - Max	18 - 77	20 - 74	18 - 77
	S.E.	1.04	1.00	0.72
Gender, n (%)	Male	90 (58.1)	84 (54.2)	174 (56.1)
	Female	65 (41.9)	71 (45.8)	136 (43.9)
Race, n (%)	White	141 (91.0)	140 (90.3)	281 (90.6)
	Black	9 (5.8)	11 (7.1)	20 (6.5)
	Asian/Pacific Islander	1 (0.6)	1 (0.6)	2 (0.6)
	Hispanic/Latino	4 (2.6)	3 (1.9)	7 (2.3)

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**APPENDIX IV-2**  
**STUDY CN138-047**  
**NUMBER OF PATIENTS RECEIVING STUDY MEDICATION**  
**BY TIME INTERVAL**

Days	Number (%) Patients				Total	
	Placebo		Aripiprazole			
Day 1 - 7	153	(100)	153	(100)	306	(100)
Day 8 - 14	145	(94.8)	145	(94.8)	290	(94.8)
Day 15 - 21	137	(89.5)	133	(86.9)	270	(88.2)
Day 22 - 28	120	(78.4)	117	(76.5)	237	(99.5)
Day 29 - 35	103	(67.3)	111	(72.5)	214	(69.9)
Day 36 - 42	95	(62.1)	106	(69.3)	201	(65.7)
Day 43 - 49	87	(56.9)	101	(66.0)	188	(61.4)
Day 50 - 56	82	(53.6)	98	(64.1)	180	(58.8)
Day 57 - 63	74	(48.4)	95	(62.1)	169	(55.2)
Day 64 - 70	66	(43.1)	94	(61.4)	160	(52.3)
Day 71 - 77	65	(42.5)	91	(59.5)	156	(51.0)
Day 78 - 84	61	(39.9)	88	(57.5)	149	(48.7)
Day 85 - 91	57	(37.3)	87	(56.9)	144	(47.1)
Day 92 - 98	53	(34.6)	85	(55.6)	138	(45.1)
Day 99 - 105	53	(34.6)	84	(54.9)	137	(44.8)
Day 106 - 112	51	(33.3)	79	(51.6)	130	(42.5)
Day 113 - 119	50	(32.7)	77	(50.3)	127	(41.5)
Day 120 - 126	50	(32.7)	76	(49.7)	126	(41.2)
Day 127 - 133	47	(30.7)	76	(49.7)	123	(40.2)
Day 134 - 140	47	(30.7)	75	(49.0)	122	(39.9)
Day 141 - 147	46	(30.1)	75	(49.0)	121	(39.5)
Day 148 - 154	46	(30.1)	74	(48.4)	120	(39.2)
Day 155 - 161	46	(30.1)	73	(47.7)	119	(38.9)
Day 162 - 168	45	(29.4)	71	(46.4)	116	(37.9)
Day 169 - 175	44	(28.8)	71	(46.4)	115	(37.6)
Day 176 - 182	44	(28.8)	71	(46.4)	115	(37.6)
Day 183 - 189	2	(1.3)	1	(0.7)	3	(1.0)

**ITEMS UTILIZED IN THE REVIEW**

**APPENDIX V-1  
ITEMS UTILIZED IN THE REVIEW**

<b>Submission Date</b>	<b>Items Reviewed</b>
December 3, 2002	CN138-047 Study Report Proposed Labeling Financial Disclosure Certification Case Report Tabulations Case Report Forms
February 20, 2003	Foreign Regulatory Update Demographic Analyses of Safety and Efficacy Data Mean Change from Baseline ECG Data Clarification of Patient Inclusion Criteria
March 28, 2003	Updated Literature Search

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**EFFICACY**

**APPENDIX VI-1: STUDY CNI38-047  
PRINCIPAL INVESTIGATORS**

Center	Investigator (Country)	Center	Investigator (Country)
003	Adam F. Lowy, MD (U.S.)	046	Janusz Janczewski, MD (Poland)
004	Mohammed Bari, MD (U.S.)	047	Mieczyslaw Janiszewski, MD (Poland)
005	David W. Brown, MD (U.S.)	048	Marek Masiak, MD (Poland)
006	Carlos Figueroa, MD (U.S.)	049	Wlodzimierz Chrzanowski, MD (Pol.)
007	Mary Ann Knesevich, MD (U.S.)	050	Yuri Popov, MD (Russia)
008	Mark Lerman, MD (U.S.)	051	Yuri L. Nuller, MD (Russia)
010	David A. Sack, MD (U.S.)	052	Alexander Mouzitchenko, MD (Russia)
011	Rajinder S. Shiwach, MD (U.S.)	053	Vladimir Tochilov, MD (Russia)
012	Tram K. Tran-Johnson, PharmD (U.S.)	054	Michail Burducovsky, MD (Russia)
022	Ivan Drabek, MD (Czech Republic)	055	Rouslan Vovin, MD, PhD (Russia)
024	Vladimir Muchl, MD (Czech Republic)	056	Alexander Kociubynsky, MD (Russia)
031	Valeriy Bitensky, MD (Ukraine)	057	Zurab Kekelidze, MD (Russia)
033	Svetlana Kazakova, MD (Ukraine)	059	Galina Panteleeva, MD (Russia)
034	Oleg Chaban, MD, PhD (Ukraine)	060	Boris Tsygankov, MD (Russia)
036	Viktor Samokhvalov, MD (Ukraine)	061	Uryi Alexandrovsky, MD (Russia)
038	Vladislav Demchenko, MD (Ukraine)		

**APPENDIX VI-2  
STUDY CN138-047  
PATIENT DISPOSITION**

Patient Status	Number of Patients (%)		
	Placebo	Aripiprazole	Total
Enrolled	n/a	n/a	372
Baseline Failures	n/a	n/a	72 <sup>a</sup>
<hr style="border-top: 1px dashed black;"/>			
Randomized	155	155	310
<b>Discontinued Double-Blind Treatment</b>			
Lack of Efficacy (Relapse)	76 (49.0)	42 (27.1)	118 (38.1)
Patient Withdrew Consent	12 (7.8)	18 (11.6)	30 (9.7)
Adverse Event <sup>b</sup>	13 (8.4)	16 (10.3)	29 (9.4)
Patient Unreliability	3 (1.9)	4 (2.6)	7 (2.3)
Lost to Follow-Up	2 (1.3)	0	2 (0.6)
Death	0	1 (0.6)	1 (0.3)
Other Known Cause <sup>c</sup>	4 (2.6)	3 (1.9)	7 (6.4)
Completed Double-Blind Treatment	45 (29.0)	71 (45.8)	116 (37.4)

**APPENDIX VI-3  
STUDY CN138-047  
SUMMARY OF CONCOMITANT CNS MEDICATION USAGE**

Class of Drug	Number (%) of Patients with Any CNS Medication			
	Placebo N = 153		Aripiprazole N = 153	
Any CNS Medication	109	(71.2)	110	(71.9)
Anxiolytic	98	(64.1)	100	(65.4)
Other Analgesic or Antipyretic	17	(11.1)	20	(13.1)
Hypnotic and Sedative	8	(5.2)	7	(4.6)
Antiepileptic	3	(2.0)	6	(3.9)
Opioid	2	(1.3)	3	(2.0)
Antimigraine Preparation	1	(0.7)	1	(0.7)

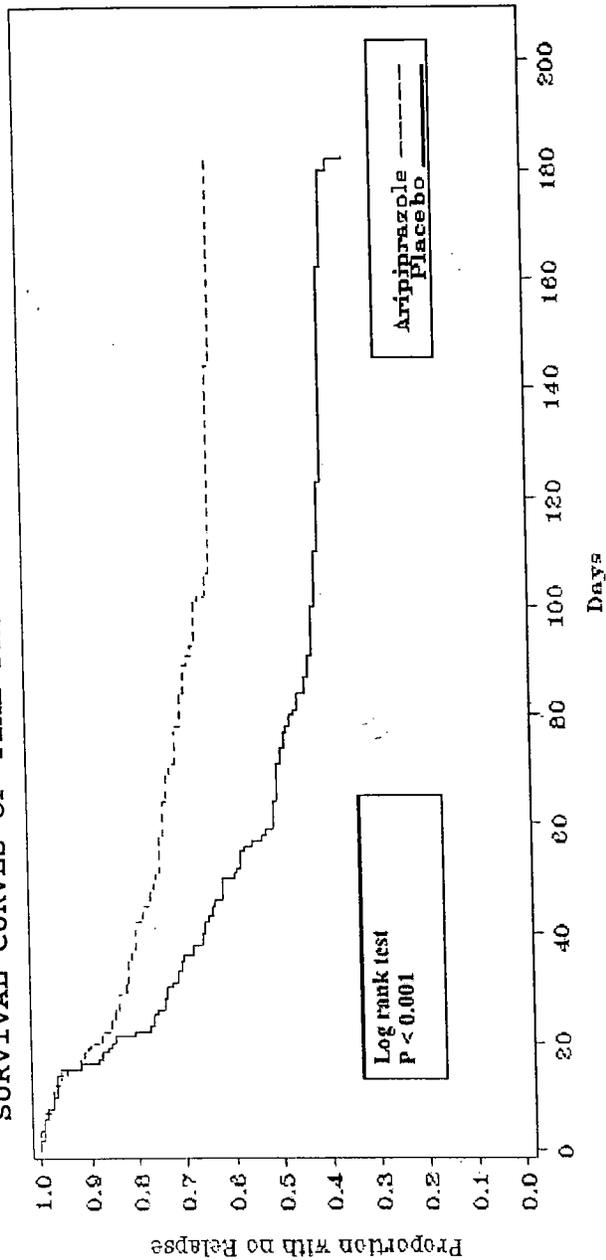
**APPENDIX VI-4  
STUDY CN138-047  
TIME FROM RANDOMIZATION TO RELAPSE**

Log Rank Test P-Value for Equality of Survival Curves: < 0.001  
Relative Risk (Aripiprazole:Placebo) 95% CI<sup>a</sup>: 0.503 (0.354, 0.714)

Study Week	Placebo N = 149		Aripiprazole N = 148	
	Percentage <sup>b</sup>	(S.E.) <sup>c</sup>	Percentage <sup>b</sup>	(S.E.) <sup>c</sup>
2	95.9	(1.64)	94.5	(1.89)
4	73.5	(3.69)	83.8	(3.10)
6	64.7	(4.03)	78.4	(3.50)
10	50.5	(4.26)	72.2	(3.85)
18	40.3	(4.24)	63.5	(4.19)
26	39.4	(4.24)	62.6	(4.22)

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APPENDIX VI-5  
STUDY CN138-047  
SURVIVAL CURVES OF TIME FROM RANDOMIZATION TO RELAPSE



**APPENDIX VI-6**  
**STUDY CN138-047**

**DEMOGRAPHIC/BASELINE SEVERITY SUBGROUP ANALYSIS OF TIME FROM RANDOMIZATION TO RELAPSE**

Variable	Subgroup	TX	N	% Not Relapsing <sup>13</sup>	Log-Rank p-value <sup>14</sup>	Hazard Ratio (95% CI) <sup>15</sup>
Gender	Males	Plac	85	42.7	0.016	0.570 (0.357, 0.910)
		Ari	78	61.5		
	Females	Plac	64	34.7	0.002	0.436 (0.257, 0.740)
		Ari	70	63.6		
Age	18-50 years	Plac	113	36.1	<0.001	0.443 (0.296, 0.665)
		Ari	113	64.7		
	>50 years	Plac	36	50.2	0.479	0.775 (0.382, 1.573)
		Ari	35	55.9		
Race	Caucasian	Plac	135	38.0	<0.001	0.449 (0.309, 0.652)
		Ari	133	64.9		
	Non-Cauc.	Plac	14	59.8	0.403	1.638 (0.510, 5.255)
		Ari	15	43.6		
Baseline PANSS Total Score	<81	Plac	72	42.1	0.002	0.462 (0.278, 0.767)
		Ari	81	68.6		
	≥81	Plac	77	36.8	0.016	0.558 (0.344, 0.906)
		Ari	67	54.9		

<sup>13</sup> Kaplan-Meier estimated survival rates at week 26.  
<sup>14</sup> P-value for equality of the aripiprazole and placebo survival curves within the subgroup.  
<sup>15</sup> Aripiprazole:Placebo hazard ratio for relapse.

**SAFETY**

**APPENDIX VII-1  
STUDY CN138-047  
SCHEDULE OF SAFETY ASSESSMENTS**

Safety Measure	Screening	Baseline	End of Week:														
			1	2	3	4	6	8	10	14	18	22	26 <sup>16</sup>				
Physical Exam	X																X
Vital Signs <sup>17</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Waist/Hip <sup>18</sup>		X															X
12-Lead ECG	X																X
Lab Tests <sup>19</sup>	X																X
Pregnancy Test	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SAS <sup>20</sup>		X															X
AIMS <sup>21</sup>		X															X
BAS <sup>22</sup>		X															X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

<sup>16</sup> Or at the time of early termination.  
<sup>17</sup> Supine and standing systolic and diastolic blood pressure and radial artery pulse rate.  
<sup>18</sup> Waist and hip circumference.  
<sup>19</sup> Routine hematology, serum chemistry, urinalysis for protein, glucose, and blood; prolactin, and glycosylated hemoglobin. Chemistry included fasting serum glucose, total cholesterol, HDL, LDL, and triglycerides.  
<sup>20</sup> Simpson Angus Scale for EPS.  
<sup>21</sup> Abnormal Involuntary Movement Scale for dyskinesia.  
<sup>22</sup> Barnes Akathisia Scale.

APPENDIX VII-2  
STUDY CN138-047

PATIENTS WITH SERIOUS ADVERSE EVENTS

TX/Patient Number	Age	Sex	Onset Day	Onset Dose (mg/day) <sup>23</sup>	Serious Adverse Event
ARIPRAZOLE					
138047-5-64	40	M	76	0	Hospitalization for psychosocial support.
138047-7-14	29	M	8	15	Hospitalization for schizophrenic exacerbation.
138047-7-117	30	M	1	15	Struck by two motor vehicles, death.
138047-7-118	51	M	66	15	Hospitalization for schizophrenic exacerbation.
138047-7-124	32	M	19	0	Hospitalization for schizophrenic exacerbation.
138047-10-5	23	M	101	15	Hospitalization for agitation.
138047-49-94	30	M	140	15	Food poisoning.
138047-49-251	49	F	42	0	Hospitalization for schizophrenic exacerbation.
138047-51-158	62	F	8	0	Breast carcinoma.
138047-56-131	50	F	30	15	Hospitalization for psychosocial support.
138047-57-339	52	M	7	15	Hospitalization due to a seizure.

<sup>23</sup> A dose of "0" for aripiprazole patients indicates that aripiprazole was discontinued before the event onset.

APPENDIX VII-2  
STUDY CN138-047  
PATIENTS WITH SERIOUS ADVERSE EVENTS

TX/Patient Number	Age	Sex	Onset Day	Onset Dose (mg/day) <sup>23</sup>	Serious Adverse Event
PLACEBO					
138047-3-10	50	M	91	0	Schizophrenic reaction.
138047-3-49	45	M	60	0	Drug abuse.
138047-7-116	56	M	180	0	Schizophrenic reaction.
138047-7-123	47	M	89	0	Pneumonia.
138047-7-370	50	M	5	0	Schizophrenic reaction.
138047-10-1	37	M	15	0	Upper respiratory infection.
138047-10-56	26	M	36	0	Schizophrenic reaction.
138047-38-319	41	M	33	0	Schizophrenic reaction.
138047-49-96	43	F	110	0	Hallucination.

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APPENDIX VII-3 STUDY CN138-047 ADVERSE EVENTS THAT LED TO DISCONTINUATION (N(%))		
Body System/Adverse Event	Placebo (N=153)	Aripiprazole (N=153)
<b>Body as a Whole</b>		
Accidental Injury	0 (0%)	1 (0.7%)
Psychosocial Support	0 (0%)	1 (0.7%)
<b>Cardiovascular System</b>		
Abnormal EKG	0 (0%)	1 (0.7%)
Bruit	0 (0%)	1 (0.7%)
Hypertension	0 (0%)	1 (0.7%)
Myocardial Ischemia	0 (0%)	1 (0.7%)
<b>Digestive System</b>		
Diarrhea	0 (0%)	1 (0.7%)
Dyspepsia	0 (0%)	2 (1.3%)
Vomiting	0 (0%)	2 (1.3%)
<b>Metabolic/Nutritional</b>		
CPK Increased	0 (0%)	1 (0.7%)
<b>Nervous System</b>		
Agitation	0 (0%)	1 (0.7%)
Anxiety	1 (0.7%)	0 (0%)
Drug Dependence	3 (2.0%)	0 (0%)
Hallucination	0 (0%)	1 (0.7%)
Insomnia	1 (0.7%)	1 (0.7%)
Neurosis	1 (0.7%)	0 (0%)
Psychosis	1 (0.7%)	1 (0.7%)
Schizophrenic Reaction	8 (5.2%)	6 (3.9%)
Seizure	0 (0%)	1 (0.7%)
Tremor	0 (0%)	1 (0.7%)
<b>Respiratory System</b>		
Coughing	0 (0%)	1 (0.7%)
Upper Resp. Infection	0 (0%)	1 (0.7%)
<b>Skin/Appendages</b>		
Rash	0 (0%)	1 (0.7%)
<b>Urogenital System</b>		
Breast Carcinoma <sup>24</sup>	0 (0%)	1 (1.4%)

<sup>24</sup> Incidence adjusted for gender.

APPENDIX VII-4 STUDY CN138-047 INCIDENCE OF TREATMENT-EMERGENT ADVERSE EVENTS (%) <sup>25</sup>		
BODY SYSTEM/ADVERSE EVENT	PLACEBO (N=153)	ARIPIPRAZOLE (N=153)
<b>Body as a Whole</b>		
Headache	12.4%	9.8%
Back Pain	<1%	2.0%
Psychosocial Support	0%	2.0%
Accidental Injury	2.6%	1.3%
Asthenia	0%	1.3%
Face Edema	<1%	1.3%
Infection	2.0%	1.3%
Pain	1.3%	1.3%
Chest Pain	0%	1.3%
Extremity Pain	<1%	1.3%
<b>Cardiovascular System</b>		
Hypertension	3.9%	2.0%
<b>Digestive System</b>		
Vomiting	3.3%	5.9%
Nausea	3.3%	5.2%
Dyspepsia	2.0%	3.9%
Dental Disorder	2.0%	3.3%
Diarrhea	0%	2.6%
Gastritis	<1%	2.0%
Appetite Increased	<1%	1.3%
Constipation	3.3%	1.3%
<b>Hemic/Lymphatic</b>		
Anemia	<1%	1.3%
Ecchymosis	<1%	1.3%
<b>Metabolic/Nutritional</b>		
Weight Loss	0%	1.3%
<b>Musculoskeletal System</b>		
Myasthenia	0%	1.3%
<b>Nervous System</b>		
Insomnia	39.9%	42.5%
Anxiety	22.2%	15.0%
Tremor	1.3%	8.5%
Akathisia	6.5%	7.8%
Agitation	7.8%	7.2%

<sup>25</sup> For those events reported in at least 1.0% of aripiprazole-treated patients.

APPENDIX VII-4 STUDY CN138-047 INCIDENCE OF TREATMENT-EMERGENT ADVERSE EVENTS (%) <sup>25</sup>		
BODY SYSTEM/ADVERSE EVENT	PLACEBO (N=153)	ARIPIPIRAZOLE (N=153)
Nervousness	5.2%	5.2%
Lightheadedness	3.3%	4.6%
Schizophrenic Reaction	6.5%	4.6%
Depression	2.0%	3.3%
Extrapyramidal Syndrome	5.2%	3.3%
Somnolence	2.0%	3.3%
CNS Stimulation	<1%	2.6%
Movement Disorder	2.0%	1.3%
Hallucination	<1%	1.3%
Extremity Tremor	<1%	1.3%
<b>Respiratory System</b>		
Upper Resp. Infection	2.0%	3.9%
Bronchitis	<1%	3.3%
Rhinitis	2.6%	3.3%
Pharyngitis	2.0%	2.0%
Coughing	3.9%	1.3%
<b>Skin/Appendages</b>		
Rash	2.6%	2.6%
Cutaneous Lesion	0%	2.0%
<b>Special Senses</b>		
Conjunctivitis	1.3%	2.0%
<b>Urogenital System<sup>26</sup></b>		
Abnormal Urine (male)	0%	1.2%
Albuminuria (male)	0%	1.2%
Breast Carcinoma (fem)	0%	1.4%
Menstrual Disorder	0%	1.4%
Dysmenorrhea	0%	1.4%
Mastopathy (fem)	0%	1.4%
Urolithiasis (male)	0%	1.2%

<sup>26</sup> Incidence adjusted for gender.

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/s/

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Greg Dubitsky  
7/10/03 03:35:58 PM  
MEDICAL OFFICER

Thomas Laughren  
8/25/03 07:45:24 AM  
MEDICAL OFFICER

We are in the process of resolving final labeling  
issues, and once this is accomplished, this supplement  
can be approved.--TPL

**MEMORANDUM**

**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH**

**DATE:** August 18, 2003

**FROM:** Thomas P. Laughren, M.D.  
Team Leader, Psychiatric Drug Products  
Division of Neuropharmacological Drug Products  
HFD-120

**SUBJECT:** Recommendation for Approval Action for  
Abilify tablets (aripiprazole) for the longer-term treatment of schizophrenia

**TO:** File NDA 21-436/S-001  
[Note: This overview should be filed with the 12-3-02  
original submission.]

**1.0 BACKGROUND**

Aripiprazole is a partial agonist at D2 and 5-HT1A receptors and an antagonist at 5HT2 receptors. This class of compounds is referred to as "dopamine system stabilizers," based on the hope that they will permit sufficient nigrostriatal DA activity to prevent EPS while at the same time reducing excessive DA activity in the mesolimbic pathways. This drug was approved for the treatment of acute schizophrenia on 11-15-02. This additional development program and supplemental NDA focus on aripiprazole's use in the longer-term treatment of schizophrenia, at a dose of 15 mg/day.

We did not have any meetings or correspondence with the sponsor regarding their program for obtaining longer-term efficacy data for the schizophrenia indication.

Since the proposal is to use the currently approved aripiprazole tablet, there was no need for chemistry, pharmacology, or biopharmaceutic reviews of this supplement. The focus was on clinical data. The primary review of the efficacy and safety data was done by Greg Dubitsky, M.D., from the clinical group. Peiling Yang, Ph.D., from the Division of Biometrics, also reviewed the efficacy data.

The study supporting this supplement was conducted under IND 42,776. The original supplement for this expanded indication was submitted 12-3-02.

We decided not to take this supplement to the Psychopharmacological Drugs Advisory Committee (PDAC).

## **2.0 CHEMISTRY**

As aripiprazole tablets are already approved, there were no CMC issues requiring review for this NDA.

## **3.0 PHARMACOLOGY**

As aripiprazole tablets are already approved, there were no pharm/tox issues requiring review for this NDA.

## **4.0 BIOPHARMACEUTICS**

As aripiprazole tablets are already approved, there were no biopharmaceutics issues requiring review for this NDA.

## **5.0 CLINICAL DATA**

### **5.1 Efficacy Data**

#### **5.1.1 Overview of Study CN138-047**

This was a 31 center study (9 US and 22 European centers), however, 1 center was closed after a discovery that it was in violation of ICH/GCP guidelines, and a decision was made prior to database lock to exclude data from this center. This study had a different design than the typical long-term efficacy study in schizophrenia, i.e., the usual trial is a randomized withdrawal design, in which patients "responding" to open treatment for an acute episode are randomized to continuation on drug or placebo and observed for time to relapse. This trial recruited adult patients ( $\geq 18$ ) who met DSM-IV criteria for schizophrenia and who by history were determined to be stable (but still symptomatic) while taking antipsychotic medications for at least 3 months. They had to have a baseline PANSS total score of at least 60, but a CGI severity score of  $\leq 4$ . After a 3-14 day screening phase, including a minimum 3-day antipsychotic washout phase, patients were randomized. This was a double-blind trial involving the assignment of these patients (1:1) to either aripiprazole 15 mg qd or placebo.

Patients were then observed for relapse over the next 26 weeks, where relapse was defined as:

- CGI-I  $\geq 5$  (minimally worse), or
- PANSS hostility or uncooperativeness item score  $\geq 5$  (moderately severe) on 2 successive days, or
- PANSS total score increased by  $\geq 20\%$

The primary outcome was time to relapse. [Note: Although the protocol specified time from randomization to relapse as the primary endpoint, the sponsor calculated time from first dosing to relapse.] Survival curves were estimated using Kaplan-Meier methodology and the log-rank test was used to compare survival distributions. The analysis was based on a modified intent-to-treat sample, i.e., all patients randomized who received at least 1 dose of assigned treatment and who had at least 1 postbaseline efficacy evaluation.

There was a slight excess of males compared to females (about 56%), the mean age was about 42, and patients were predominantly white (about 90%). The mean baseline PANSS total scores were about 82 (i.e., although stable, these patients were quite symptomatic at baseline). About 45% of patients were on inpatient status at baseline.

A total of n=310 patients were randomized (n=155 to aripiprazole and n=155 to placebo). The original protocol provided for n=250 patients to be randomized, however, due to very rapid accrual, n=310 patients were randomized within the first 2 months of starting the study (The protocol was amended [#3] to permit greater enrollment). The intent-to-treat sample included a total of n=297 patients (n=148 for aripiprazole and n=149 for placebo).

The overall rates of discontinuation prior to reaching the 26 week endpoint were as follows:

Aripiprazole: 84/155 (54%)  
Placebo: 110/155 (71%)

The results on the primary endpoint, time to relapse, favored aripiprazole:

Hazard ratio (aripiprazole vs placebo) = 0.503 (p < 0.001)

The proportion relapsed by 26 weeks also favored aripiprazole over placebo:

Aripiprazole: 50/148 (34%)  
Placebo: 85/149 (57%)      p < 0.001

Dr. Yang did an additional analysis to correct for certain discrepancies in the sponsor's analysis:

-As noted, the sponsor's calculations were based on time from first dosing to relapse; Dr. Yang did the analysis for time of randomization to relapse.

-Dr. Yang found several patients for whom the actual relapse date was different than that specified by the sponsor.

-Dr. Yang included 6 patients excluded by the sponsor due to failure to meet inclusion/exclusion criteria.

-With all of these changes incorporated, Dr. Yang's re-analysis still strongly favored aripiprazole over placebo:

Hazard ratio (aripiprazole vs placebo) = 0.537 (p < 0.001)

Exploratory analyses looking at the effect of age, sex, and race did not suggest that any of these factors affected the outcome.

Comment: Both Drs. Dubitsky and Yang considered this a positive study in support of a claim of long-term efficacy for aripiprazole in schizophrenia, and I agree.

### **5.1.2 Conclusions Regarding Efficacy Data**

Study CN138-047 demonstrated a benefit of aripiprazole over placebo for the maintenance of response in patients with schizophrenia who, by history, had been stable on antipsychotic treatment for  $\geq 3$  months and who were then observed for relapse during a 26-week followup period.

### **5.2 Safety Data**

Dr. Dubitsky reviewed the safety data for study CN138-047 (including data for n=153 patients exposed to aripiprazole and n=153 patients exposed to placebo) in this supplement. In summary, there were no important new safety concerns identified in association with the longer-term use of aripiprazole that had not already been observed in short-term use. One interesting finding was additional support for a finding observed in the premarketing safety database of a tendency for aripiprazole to actually shorten the QTc interval and slow the heart rate slightly compared to placebo.

### **5.3 Clinical Sections of Labeling**

We have modified the language in the 4 sections of labeling in which the sponsor has proposed changes, i.e., Clinical Trials, Indications, Adverse Reactions, and Dosage and Administration. As of 8-11-02, we reached agreement with Otsuka/BMS on the language for labeling.

## **6.0 WORLD LITERATURE**

A literature search for aripiprazole was conducted by the sponsor, covering a period from 1-1-02 through 2-3-03. This search identified 66 additional papers not revealed in previous searches, and the sponsor warranted that these papers contained no findings that would adversely affect conclusions about the safety of aripiprazole.

## **7.0 FOREIGN REGULATORY ACTIONS**

To my knowledge, aripiprazole is not approved for the longer-term treatment of schizophrenia anywhere at this time.

## **8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING**

As noted, we did not take this supplement to the Psychopharmacological Drugs Advisory Committee (PDAC).

## **9.0 DSI INSPECTIONS**

Two sites from study CN138-047 (Knesevich and Sack) were inspected. The Knesevich site received a rating of NAI and the Sack site received a VAI rating, for some minor deficiencies. Overall, there was no concern about the efficacy data coming from either site.

## **10.0 LABELING AND APPROVAL LETTER**

### **10.1 Labeling Attached to Approval Package**

Our mutually agreed upon labeling for this new claim is included in the approval letter.

### **10.2 Foreign Labeling**

To my knowledge, aripiprazole is not approved for the longer-term treatment of schizophrenia anywhere at this time.

## **11.0 CONCLUSIONS AND RECOMMENDATIONS**

I believe that Otsuka/BMS has submitted sufficient data to support the conclusion that aripiprazole is effective and acceptably safe in the longer-term treatment of schizophrenia. Since we have now reached agreement with Otsuka/BMS on final labeling, I recommend that we issue the attached approval letter with the agreed upon labeling language for this expanded claim.

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cc:  
Orig NDA 21-436/S-001  
HFD-120  
HFD-120/TLaughren/RKatz/GDubitsky/SHardeman

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/s/

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Thomas Laughren  
8/18/03 01:40:13 PM  
MEDICAL OFFICER

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 21-436/S-001**

**STATISTICAL REVIEW(S)**



DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

**STATISTICAL REVIEW AND EVALUATION**  
**PHASE IV COMMITMENT**

**NDA No./SUPPLEMENT:** 21-436 / <sup>SE1</sup>~~SE6~~-001  
**DATE RECEIVED BY THE CENTER:** December 3, 2002  
**DRUG NAME:** Abilify® (aripiprazole)  
**APPLICANT:** Bristol-Myers Pharmaceutical Research Institute  
**INDICATION:** Treatment of stabilized patients with chronic schizophrenia  
**DOCUMENTS REVIEWED:** \\Cdsub1\n21436\S\_001\2002-12-03\crt  
\\Cdsub1\n21436\S\_001\2003-02-12\crt  
**BIOMETRICS DIVISION:** **DIVISION OF BIOMETRICS I (HFD-710)**  
**REVIEWING STATISTICIAN:** Peiling Yang, Ph.D.  
**CONCURRING REVIEWERS:** Kun Jin, Ph.D.,  
George Chi, Ph.D.  
**MEDICAL DIVISION:** **NEUROPHARM DRUG PRODUCTS (HFD-120)**  
**PROJECT MANAGER:** Mr. Steve Hardeman  
**MEDICAL OFFICER:** Gregory Dubitsky, M.D.  
**DIVISION DIRECTOR:** Russell Katz, M.D.

**DISTRIBUTION: NDA 21,436/SE6-001**

HFD-120/Mr. Steve Hardeman  
HFD-120/Dr. Gregory Dubitsky, M.D.  
HFD-120/Dr. Thomas Laughern, M.D.  
HFD-710/Dr. Peiling Yang  
HFD-710/Dr. Kun Jin  
HFD-710/Dr. George Chi  
HFD-700/Dr. Charles Anello

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# 1 EXECUTIVE SUMMARY AND STATISTICAL FINDINGS

## 1.1 CONCLUSIONS AND RECOMMENDATIONS

There was statistically significant evidence that the aripiprazole group was associated with longer times to relapse as compared to the placebo group. One of the criteria used in defining relapse “PANSS score  $\geq 5$  on hostility or uncooperativeness” was problematic [ ]

## 1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

Aripiprazole was approved in November 2002 for the treatment of patients with schizophrenia. The Approval letter requests the sponsor submit the results of Study CN138-047 to address the longer-term efficacy of aripiprazole in the treatment of adults with schizophrenia. The purpose of this submission is to fulfill this post approval commitment and propose the revisions to the approved labeling for this NDA based on the outcomes of this Study.

Study CN138-047 was a multi-center, randomized, double-blinded study. The primary endpoint was time to relapse. Patients were to receive either aripiprazole or placebo for 26 weeks. Patients who had completed the treatment phase or who had discontinued after at least 2 weeks of double-blind treatment due to lack of efficacy could enter an optional open-label extension. This review only evaluated results of the 26-week double-blinded study.

## 1.3 PRINCIPAL FINDINGS

**Overall Evidence:** There was statistically significant evidence that the aripiprazole group was associated with longer times to relapse as compared to the placebo group. The p-value for testing against the null hypothesis of equal time-to-relapse curves in favor of unequal time-to-relapse curves was less than 0.001 and the hazard ratio (aripiprazole/placebo) was estimated to be 0.537 with a 95% confidence interval of (0.385, 0.748). This indicated that under the assumption of a constant hazard ratio, the instantaneous risk for an aripiprazole patient to relapse was estimated to be 53.7% of that for a placebo patient given that the patient had not yet relapsed. The probabilities of not experiencing relapse by week 26 were estimated to be 35.7% for the placebo and 58.9% for the aripiprazole groups.

**Subgroup Analysis:** There were no inconsistent findings between subgroups.

**Label Issue:** Three criteria (CGI-I score  $\geq 5$ , PANSS score  $\geq 5$  on the item of hostility or uncooperativeness on 2 successive days,  $\geq 20\%$  increase in PANSS total scores) were used in defining relapse. It was noted, however, relapse was rarely based on the criterion of PANSS score  $\geq 5$  on hostility or uncooperativeness. In addition, for those who relapsed by this criterion, there was no recorded score for the following day as required for confirmation. [ ]

## 2 INTRODUCTION

### 2.1 OVERVIEW

#### 2.1.1 Background

Reference is made to the Approval Letter dated November 15, 2002 for the Supplemental New Drug application 21-436/SE6-001 supporting the use of aripiprazole for the treatment of patients with schizophrenia. Reference is also made to the post approval commitment to submit the results of Study CN138-047 to address the longer-term efficacy of aripiprazole in the treatment of adults with schizophrenia. The purpose of this submission is to fulfill this post approval commitment and propose the revisions to the approved labeling for this NDA based on the outcomes of CN138-047.

#### 2.1.2 Major Statistical Issues

A major statistical issue that could have  is described as below.  
Three criteria were used in defining relapse with one of the criteria being "PANSS score  $\geq 5$  on the Item of Hostility or Uncooperativeness". Relapse by this criterion required maintenance of the score on two successive days. Very few patients relapse by this criterion and for those by this criterion there was no recorded score for the following day. Nonetheless, the sponsor considered these patients as relapsing on the first day of such a score without meeting the formal criteria. There were only 2 patients in each arm who relapsed solely based on this criterion (but without the following day confirmation).

### 2.2 DATA SOURCES

Data used for review are from the electronic submission received on December 3, 2002. The network path is "\\Cdsesub1\n21436\S\_001\2002-12-03\datasets" in the EDR.

## 3 STATISTICAL EVALUATION

### 3.1 EVALUATION OF EFFICACY

#### 3.1.1 Protocol Title

The protocol for this trial is titled "*A multicenter, randomized, double blind, placebo controlled, 26 week study of a fixed dose of aripiprazole in the treatment of stabilized patients with chronic schizophrenia*".

### 3.1.2 Study Objectives

The primary objective of this study was to compare the time from randomization to relapse between treatment with aripiprazole 15 mg/day and treatment with placebo over a 26 weeks in stabilized patients with chronic schizophrenia. Secondary objectives were to assess the efficacy, safety and tolerability of aripiprazole relative to placebo in stabilized patients with chronic schizophrenia.

### 3.1.3 Study Design

This was a multicenter, randomized, double-blind, parallel, placebo-controlled study. Subjects underwent screening evaluations to determine eligibility prior to study enrollment. After 3-14 days screening phase including a minimum 3-day neuroleptic washout, each patient was randomly assigned in 1:1 ratio to receive either placebo or aripiprazole (15-mg dose daily) for 26 weeks. Patients who had completed the treatment phase or who had discontinued after at least 2 weeks of double-blind treatment due to lack of efficacy could enter an optional 52-week open-label extension phase<sup>1</sup>.

### 3.1.4 Efficacy Endpoints

#### 3.1.4.1 Primary Endpoint

- **Time from randomization to relapse.** Relapse was defined as one or more of the following:
  - Clinical Global Impression of Improvement (CGI-I) score of  $\geq 5$  (minimally worse), or
  - Positive and Negative Syndrome Scale (PANSS) score of  $\geq 5$  (moderately severe) on the items of hostility or uncooperativeness on 2 successive days, or
  - $\geq 20\%$  increase in the PANSS Total score.

CGI-I was rated based on the degree of improvement compared with the baseline CGI-S (CGI severity of illness) score. The degree of improvement was rated on 7-point scale with a higher score indicating worse improvement. The PANSS consisted of three subscales:

- Positive Subscale: 7 positive symptom (including hostility) constructs;
- Negative Subscale: 7 negative symptom constructs;
- General Psychopathology Subscale: 16 symptom (including uncooperativeness) constructs.

The severity of each symptom in each subscale of the PANSS was also rated on a 7-point scale with a higher score indicating more severe. Both PANSS and CGI were to be rated by the same rater for a given patient.

---

<sup>1</sup> In the extension phase, patients received either aripiprazole 15-30 mg per day or olanzapine 10-20 mg per day.

Per protocol, the schedule for the CGI assessment was more intense than that for the PANSS assessment. After baseline, the CGI was rated at the end of weeks 1, 2, 3, 4, 6, 8, 10, 14, 18, 22, 26 and the PANSS was rated only at the end of weeks 3, 6, 10, 18, 26. However, patients were clinically supervised daily to assess possible worsening of symptoms and the need for an unscheduled evaluation. In addition, if a patient discontinued before the end of the study, both CGI and PANSS were to be rated within 24 hours after the last dose of study medication, or as soon as possible. Patients who did not relapse were censored on the latest of the date of their date of last efficacy evaluation, the date of their last dose of study medication or the date of dropout.

#### 3.1.4.2 Secondary Endpoints

- Number of relapses;
- Mean change from randomization to Week 26 on the:
  - PANSS Negative Subscale scores,
  - PANSS Total, Negative Subscale and PANSS Positive Subscale scores,
  - CGI Severity scores;
- CGI Improvement;
- Time to discontinuations for lack of efficacy (LOE);
- Time to discontinuations for lack of efficacy (LOE) or adverse events (AE);
- Mean change from randomization to Week 6 on the PANSS Total, PANSS negative Subscales and PANSS Positive Subscale scores.

#### 3.1.5 Sample Size Considerations

The sample size estimation was based on the following information postulated at the design stage.

- a 1:1 ratio between the two arms;
- a 6-month relapse rate of 55% for the placebo arm and 32% for the aripiprazole arm;
- a 10% dropout rate;
- an accrual period of 3 months and a study duration of 6 months after the end of accrual;
- a two-sided significance level ( $\alpha$ ) of 0.05 and a power ( $1-\beta$ ) of 90%;
- an exponential distribution for the relapse times and a hazard ratio of 2.07 (placebo/ aripiprazole).

These led to a total of 180 evaluable patients (90 in each arm) and a total of 86 events required for the primary analysis. A total of 194 patients would have to be randomized to account for dropout.

In Amendment #3 to the study protocol, the number of enrollments was increased to 300 with the expectation that 244 patients would be randomized.

### 3.1.6 Efficacy Analysis Methods (Per Protocol)

The sponsor defined 3 samples where analyses were performed:

- **Randomized Sample:** all patients who were randomized to double-blind treatment;
- **Safety Sample:** those patients in the Randomized Sample who received at least one dose of study medication as indicated on the dosing record;
- **Efficacy Sample:** those patients in the Safety Sample who had at least one post-randomization efficacy evaluation.

#### 3.1.6.1 Primary Endpoint

The primary endpoint was time to relapse, with the primary analysis being the logrank test on the Efficacy Sample. Kaplan-Meier estimates were to be used to summarize the time-to-relapse curves for the two groups.

#### 3.1.6.2 Secondary Endpoints

Mean changes from randomization to Week 6 and Week 26 on the

- PANSS Negative scores,
- PANSS Total scores,
- PANSS Positive scores, and
- CGI Severity scores

were to be evaluated respectively using analysis of covariance (ANCOVA) adjusting for randomization score. CGI Improvement and the number of relapses were to be evaluated respectively using the Cochran-Mantel-Haenszel (CMH) test. These analyses mentioned above were also to be performed at each specified study week and were to be performed on the Efficacy Sample using both Last-Observation-Carried-Forward (LOCF) and Observed-Cases (OC) data sets.

Time to discontinuations for LOE and time to discontinuations for LOE/AE were to be summarized by Kaplan-Meier estimates and evaluated using logrank test on the Safety Sample.

### 3.1.7 Sponsor's Results and Reviewer's Findings/Comments

#### 3.1.7.1 Data Sets

Although the amended protocol indicated that 250 patients would be enrolled with the expectation that 194 patients would be randomized, 372 patients were actually enrolled in 31 centers between December 21, 2000 and February 14, 2001. The extra number of accrual was due to rapid entry of patients in the weeks prior to the close of enrollment in the original 2-month accrual period. Of those enrolled, 310 patients were randomized between the treatment arms, 306 patients were included in the sponsor's Safety Sample and 297 in the Efficacy Sample (Table 1). The last patient visit occurred on August 20, 2001.

**Table 1: Sponsor's Summary of Number of Patients in Samples**

Sample	Placebo	Aripiprazole	Total
Randomized	155	155	310
Safety	153	153	306
Efficacy	149	148	297

Protocol CN138-047  
Source: Appendix 8.1.1

**Reviewer's Comments:**

- [1] The sponsor excluded from the Efficacy Sample 6 patients (all from Center 48 with 3 from each arm) who were randomized but did not meet inclusion/exclusion criteria. Since these patients had at least one post-randomization efficacy evaluation, per protocol they should have been included in the Efficacy Sample. This resulted in this reviewer's Efficacy Sample of 303 patients (152 from placebo and 151 from the aripiprazole arms).
- [2] Table 2 is this reviewer's summary of numbers of patients within centers/countries based on this reviewer's Efficacy Sample. As indicated in this table, this study was conducted in 5 countries, 49% (149/303) of the patients participated the study in Russia and only 18% (55/303) of the patients did in U.S.A. Although the majority of patients were from Russia, a descriptive summary of time-to-relapse by country suggested higher proportions of patients with relapse in the placebo group within each country (ref. Section 4.4).

**Table 2: List of Study Centers and Number of Patients (Reviewer's Efficacy Sample)**

Country	No. of Centers (No. Patients)	Study Center (No. of Patients)
U.S.A.	9 (55)	003 (4), 004 (7), 005 (5), 006 (4), 007 (13), 008 (1), 010 (13), 011 (4), 012 (4)
Czech Republic	2 (14)	022 (10), 024 (4)
Ukraine	5 (37)	031 (14), 033 (5), 034 (0), 036 (10), 038 (8)
Poland	4 (48)	046 (17), 047 (8), 048 (6), 049 (17)
Russia	11 (149)	050 (14), 051 (16), 052 (12), 053 (10), 054 (20), 055 (14), 056 (20), 057 (10), 059 (11), 060 (10), 061 (12)

### 3.1.7.2 - Protocol Deviations/Violations

The sponsor reported that 66 patients had protocol deviations/violations. Detailed deviations/violations were listed in Table 7.3 in the sponsor's Study Report.

#### Reviewer's Comments:

- [1] Table 3 is this reviewer's summary of these 66 deviators/violators by country and by randomized treatment. Within each country, there appeared a higher proportion of deviators/violators in the placebo group compared to the aripiprazole group based on this reviewer's Efficacy Sample. The overall proportions of deviators/violators across countries were 30.3% in the placebo and 13.2% in the aripiprazole groups. Despite of higher proportions of deviators/violators in the placebo group, an exploratory analysis of time-to-relapse with exclusion of these patients indicated consistent results with those of the primary analysis (ref. Section 3.1.7.5.2).

**Table 3: Reviewer's Summary of Numbers of Patients with Protocol Deviations/Violations (Reviewer's Efficacy Sample)**

Country	Placebo	Aripiprazole	Combined
U.S.A.	12/27 (= 44.4%)	10/28 (= 35.7%)	22/56 (= 39.3%)
Czech Republic	2/7 (= 28.6%)	0/7 (= 0%)	2/14 (= 14.3%)
Ukraine	6/18 (= 33.3%)	3/19 (= 15.8%)	9/37 (= 24.3%)
Poland	8/24 (= 33.3%)	3/24 (= 12.5%)	11/48 (= 22.9%)
Russia	18/76 (=23.7%)	4/73 (=5.5%)	22/149 (=14.8%)
Total	46/152 (= 30.3%)	20/151 (= 13.2%)	66/303 (=21.8%)

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### 3.1.7.3 Patient Disposition

Table 4 is the sponsor's summary of patient disposition. It appeared that a higher proportion of patients discontinued the double-blind treatment in the placebo group compared to the aripiprazole group (71.0% vs. 54.2%).

**Table 4: Sponsor's Summary of Disposition of Patients**

Patient Status	Number of Patients (%)		
	Placebo	Aripiprazole	Total
Enrolled	n/a	n/a	372
Baseline Failures	n/a	n/a	72 <sup>a</sup>
<hr/>			
Randomized	155	155	310
Discontinued Double-Blind Treatment	110 (71.0)	84 (54.2)	194 (62.6)
Lack of Efficacy (Relapse)	76 (49.0)	42 (27.1)	118 (38.1)
Patient Withdrew Consent	12 (7.8)	18 (11.6)	30 (9.7)
Adverse Event <sup>b</sup>	13 (8.4)	16 (10.3)	29 (9.4)
Patient Unreliability	3 (1.9)	4 (2.6)	7 (2.3)
Lost to Follow-Up	2 (1.3)	0	2 (0.6)
Death	0	1 (0.6)	1 (0.3)
Other Known Cause <sup>c</sup>	4 (2.6)	3 (1.9)	7 (6.4)
Completed Double-Blind Treatment	45 (29.0)	71 (45.8)	116 (37.4)

Protocol CN138-047

Source: Appendix 8.1.1

<sup>a</sup> Ten patients were baseline failures but were randomized in error (138047-36-304, 138047-36-305, 138047-36-306, 138047-48-75, 138047-48-78, 138047-48-80, 138047-48-85, 138047-48-139, 138047-48-141, and 138047-61-183). See Table 8.2C.

<sup>b</sup> Includes six patients from Center 48 who withdrew due to AE during the double-blind treatment phase (Patients 138047-48-75, 138047-48-78, 138047-48-80, 138047-48-85, 138047-48-139, and 138047-48-141) and patient 138047-49-52. These patients were excluded from the Efficacy Sample (three per group).

<sup>c</sup> Other known causes included laboratory abnormalities, positive cannabinoid screening, anemia, noncompliance with study medication, and randomization in error.

#### Reviewer's Comments:

- [1] It is noted from this table that most of the patients who discontinued the study were those who experienced relapse. This is because patients were to be immediately withdrawn from the study if a relapse occurred.
- [2] An exploratory analysis of time-to-relapse by considering those dropouts without relapse as having relapse on the date of dropout (also known as "all-cause analysis" in Division of Neuropharm Drug Products) indicated consistent results with those of the primary analysis (ref. Section 3.1.7.5.2).

### 3.1.7.4 Baseline Characteristics

Table 5 is the sponsor's summary of demographic characteristics for the Randomized Sample, based on which the treatment groups appeared comparable with respect to age, gender, race, and weight. Table 6 is the sponsor's summary of Baseline Ratings for the Randomized Sample, based on which the two groups appeared similar for each rating scale at the end of the baseline period.

**Table 5: Sponsor's Summary of Demography Characteristics (Randomized Sample)**

Variable		Placebo	Aripiprazole	Total
		N = 155	N = 155	N = 310
Age (years)	Mean	41.7	42.2	42.0
	Median	41.0	42.0	42.0
	Min - Max	18 - 77	20 - 74	18 - 77
	S.E.	1.04	1.00	0.72
Gender, n (%)	Male	90 (58.1)	84 (54.2)	174 (56.1)
	Female	65 (41.9)	71 (45.8)	136 (43.9)
Race, n (%)	White	141 (91.0)	140 (90.3)	281 (90.6)
	Black	9 (5.8)	11 (7.1)	20 (6.5)
	Asian/Pacific Islander	1 (0.6)	1 (0.6)	2 (0.6)
Weight (kg)	Mean	75.0	75.0	75.0
	Median	71.0	72.0	71.3
	Min - Max	40.5 - 150.5	43.8 - 157.3	40.5 - 157.3
	S.E.	1.46	1.59	1.08
	Missing	1	1	2

Protocol CN138-047

Source: Appendices 8.3.1, 12.8.1

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**Table 6: Sponsor's Summary of End of Baseline Ratings (Randomized Sample)**

		Placebo N = 155	Aripiprazole N = 155	Total N = 310
PANSS Total Score	Mean	82.3	81.2	81.8
	Median	82.0	80.0	80.5
	Min - Max	61 - 119	59 - 122	59 - 122
	S.E	0.91	0.98	0.67
PANSS Positive Subscale Score	Mean	16.8	16.9	16.9
	Median	16.0	17.0	16.0
	Min - Max	9 - 34	9 - 34	9 - 34
	S.E	0.36	0.38	0.26
PANSS Negative Subscale Score	Mean	23.8	23.6	23.7
	Median	24.0	23.0	24.0
	Min - Max	11 - 35	10 - 43	10 - 43
	S.E	0.36	0.38	0.26
PANSS-Derived BPRS Core Score	Mean	11.1	11.0	11.1
	Median	11.0	11.0	11.0
	Min - Max	5 - 23	5 - 21	5 - 23
	S.E	0.26	0.28	0.19
CGI Severity of Illness Score <sup>a</sup>	Mean	3.5	3.5	3.5
	Median	4.0	3.0	4.0
	Min - Max	1 - 6	1 - 6	1 - 6
	S.E	0.06	0.06	0.04

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Source: Appendices 10.2.4, 10.2.8

<sup>a</sup> Includes protocol violators with a CGI Severity Score ≤ 4.

**Reviewer' Comments and Analyses:**

- [1] One of the definitions for relapse was CGI-I score ≥ 5. The CGI-I score was the rating of the degree of improvement compared with the baseline CGI-S score (ref. Section 3.1.4.1). Based on the sponsor's summary, the median baseline CGI-S score was 4 in the placebo and 3 in the aripiprazole groups. Since the CGI-S scores might have influence on the CGI-I scores, this reviewer obtained a descriptive summary of the baseline CGI-S scores as in Table 7. As indicated in this table, a slightly numerically higher proportion of patients in the placebo group had a baseline CGI-S score ≥ 4 as compared to the aripiprazole group ((81+3)/152 = 55.3% vs. (67+5)/151 = 47.7%). Despite of this observation, a descriptive summary analysis of time-to-relapse by CGI-S score subgroups (<3 vs. ≥ 4) suggested higher proportions of patients with relapse in the placebo group within CGI-S score subgroups (ref. Section 4.4).

**Table 7: Reviewer's Summary of End of Baseline CGI-Severity Score (Reviewer's Efficacy Sample)**

CGI-Severity Score at Baseline	Placebo (N = 152)	Aripiprazole (N = 151)	Combined (N = 303)
≤ 2	5 (3.3%)	4 (2.6%)	9 (3.0%)
3	63 (41.4%)	75 (49.7%)	138 (45.5%)
4	81 (53.3%)	67 (44.4%)	148 (48.8%)
≥ 5	3 (2.0%)	5 (3.3%)	8 (2.6%)

### 3.1.7.5 Analysis of Primary Endpoint (Time to Relapse)

#### 3.1.7.5.1 Sponsor's Results

From the sponsor's Kaplan-Meier plot of time-to-relapse curves (ref. Figure 1), it appears that the two curves deviated from each other and the curve for the aripiprazole arm consistently lied above the other except during the very early time period. The sponsor's analysis results (ref. Table 8) supported this visual observation. The p-value based on the two-sided logrank test was less than 0.001, indicating statistically significant evidence for different times to relapse between the two treatment arms. Under the assumption of a constant hazard ratio, the hazard ratio<sup>2</sup> (aripiprazole / placebo) was estimated to be 0.503 with a 95% confidence interval of (0.354, 0.714). The above numerical results indicated (a) that the aripiprazole group was associated with longer times to relapse as compared to the placebo group, and (2) that the instantaneous risk for an aripiprazole patient to relapse was estimated to be 50.3% of that for a placebo patient given that the patient had not yet relapsed. The Kaplan-Meier estimated probability of not experiencing relapse at week 26 were 0.394 for the placebo group and 0.626 for the aripiprazole group (ref. Table 8). The median time to relapse was not reported by the sponsor because it was not estimable in the aripiprazole group (not enough patients relapsed).

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<sup>2</sup> Statistically, it should be called the hazard ratio, not the relative risk as in the sponsor's table. Both measure different quantities. The hazard ratio is typically used in analysis of time-to-event; it is the ratio of the hazard rates, where the hazard rate is instantaneous risk of relapse given that the patient had not yet experienced relapse. The relative risk is typically used in analysis of categorical data; it is the ratio of the risks by a certain time point.

**Table 8: Sponsor's Results of Time to Relapse (Sponsor's Efficacy Sample)**

Log Rank Test P-Value for Equality of Survival Curves:	< 0.001			
Relative Risk (Aripiprazole:Placebo) 95% CI <sup>a</sup> :	0.503 (0.354, 0.714)			
	Placebo N = 149		Aripiprazole N = 148	
Study Week	Percentage <sup>b</sup> (S.E.) <sup>c</sup> of Patients Not Experiencing Relapse <sup>d</sup>			
2	95.9	(1.64)	94.5	(1.89)
4	73.5	(3.69)	83.8	(3.10)
6	64.7	(4.03)	78.4	(3.50)
10	50.5	(4.26)	72.2	(3.85)
18	40.3	(4.24)	63.5	(4.19)
26	39.4	(4.24)	62.6	(4.22)

Protocol CN138-047

Source: Appendices 10.1.1, 10.1.2, 10.1.3, 10.1.5

NOTE: Median time to relapse and 95% CIs were not reported as they were not estimable in the aripiprazole group.

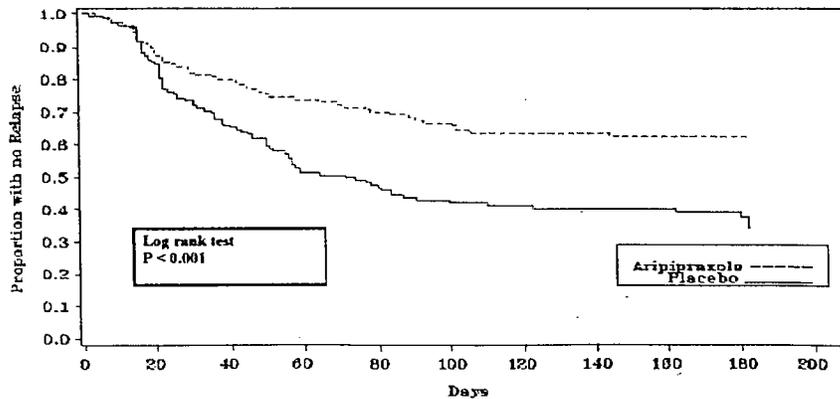
<sup>a</sup> Cox's proportional hazards model.

<sup>b</sup> Kaplan-Meier estimated survival rates.

<sup>c</sup> Standard errors using Greenwood's formula obtained from PROC LIFETEST.

<sup>d</sup> Relapse is defined as one or more of the following: a CGI-I score of  $\geq 5$  (minimally worse), or PANSS score of  $\geq 5$  (moderately severe) on the items of hostility or uncooperativeness on 2 successive days, or  $\geq 20\%$  increase in the PANSS Total Score.

**Figure 1: Sponsor's Kaplan-Meier Plot of Time to Relapse (Sponsor's Efficacy Sample)**



Protocol CN138-047

Source: Appendices 10.1.1, 10.1.2, 10.1.3

### 3.1.7.5.2 Reviewer's Comments and Results

This reviewer confirmed that the aripiprazole group was associated with longer times to relapse as compared to the placebo group, but obtained slightly different numerical results as summarized in Table 9 due to the following reasons:

- [1] Although the primary study objective was to assess the time from randomization to relapse (i.e., date of relapse - **date of randomization** + 1), it was actually calculated by the sponsor from the date of first dose to relapse (i.e., date of relapse - **date of first dosing** + 1). In 10 patients (5 in each treatment group) these two dates differed by more than 2 days. In this reviewer's analyses, the time from randomization to relapse was utilized.
- [2] There was inconsistency in the date of relapse in some patients between the sponsor's data and this reviewer's evaluation. The date of relapse was defined as the earliest date of the dates on which patients met at least one of the criteria for relapse:
  - CGI-I score  $\geq 5$ ,
  - PANSS score  $\geq 5$  on the item of hostility or uncooperativeness (corresponding to variables ppos7 and ppy8, respectively) on 2 successive days,
  - at least 20% increase in PANSS total score.

For each patient, dates for each assessment along with scores were included in the sponsor's data set. In addition, whether or not patients experienced relapse and the relapse date, if occurred, were directly recorded in the data set. The relapse date derived by this reviewer differed from the sponsor's in some patients. There were apparently recording errors in the sponsor's data set.

- [3] The number of patients in the sponsor's Efficacy Sample differed from this reviewer's Efficacy Samples. The latter included 6 more patients than the former. Since these 6 patients did not meet inclusion/exclusion criteria, they were excluded from the sponsor's Efficacy Sample. It is to be noted that per protocol Efficacy Sample should consist of all patients who had baseline and at least one post-randomization evaluation regardless of meeting the inclusion/exclusion criteria. Such a population is often called a modified intent-to-treat population and is typically the primary population for the primary efficacy evaluation in NDA review of a neuropharm drug product.

As seen in Table 9, 303 patients (152 in the placebo and 151 in the aripiprazole groups) were included in this reviewer's Efficacy Sample. A total of 149 patients (92 in the placebo and 57 in the aripiprazole groups) experienced relapse by the end of the study. The p-value from the logrank test was less than 0.001 and the estimated hazard ratio (aripiprazole / placebo) was 0.537 with a 95% confidence interval of (0.385, 0.748). The above numerical results indicated (1) that the aripiprazole group was associated with longer times to relapse compared to the placebo group, and (2) that the instantaneous risk for an aripiprazole patient to relapse was estimated to be 53.7% of that for a placebo patient given that the patient had not yet relapsed. The Kaplan-Meier probabilities of not experiencing relapse based on this reviewer's evaluation were listed in Table 10 for some time points. For example, the probabilities of not experiencing relapse by week 26 were estimated to be 35.7% for the placebo and 58.9% for the aripiprazole groups.

Relapse based on reaching PANSS score  $\geq 5$  on the item of hostility or uncooperativeness required maintenance of the score on two successive days. This reviewer noted that for patients

who had a score  $\geq 5$  on either of these two items on a given day, there was no recorded score for the following day. Nonetheless, the sponsor considered these patients as relapsing on the first day of such a score without meeting the formal criteria. Despite of this, very few patients (2 in each arm) relapsed solely based on this criterion. For more detailed discussion, please refer to Section 3.1.7.6.2.

A total of 154 patients (60 from the placebo and 94 from the aripiprazole groups) did not relapse during the study as summarized in Table 9. Of those who did not relapse, a total of 117 patients (50 from the placebo and 67 from the aripiprazole groups) discontinued the study before reaching the end of 26 weeks and before the study ended. This reviewer performed an exploratory analysis of time-to-discontinuation for these 117 patients; the results did not appear imbalance between the two treatment groups. This reviewer further performed an exploratory analysis of time-to-relapse based on the logrank test by treating these 117 patients as experiencing relapse on the discontinuation date (also known as "all-cause analysis" in Division of Neuropharm Drug Products); the results (p-value = 0.0013) were similar to those of the primary analysis (p-value < 0.001).

The sponsor reported 66 patients with protocol deviation/violation as discussed in Section 3.1.7.2. In order to investigate whether these patients had influence on efficacy results, this reviewer performed an exploratory analysis of time-to-relapse on this reviewer's Efficacy Sample but with these patients excluded. The results were consistent with those based on the primary population.

Because of rapid accrual rate, there were a total of 149 patients relapsed as compared to the planned number of events (86) in the protocol. An exploratory analysis indicated consistent results had only 86 patients relapsed.

**In conclusion**, despite of several issues raised above, this reviewer's results were consistent with the sponsor's.

**Table 9: Reviewer's Results of Time to Relapse (Reviewer's Efficacy Sample)**

	Placebo (N = 152)	Aripiprazole (N = 151)	Combined (N = 303)
# of Patients who did not relapse during the study	<b>60 (39.5%)</b>	<b>94 (62.3%)</b>	<b>154 (50.8%)</b>
(1) Discontinued before the end of Week 26 and before the end of study	50 (32.9%)	67 (44.4%)	117 (38.6%)
(2) Stayed through the end of Week 26 or the end of study	10 (6.6%)	27 (17.9%)	37 (12.2%)
# of Patients Who Relapsed	<b>92 (60.5%)</b>	<b>57 (37.7%)</b>	<b>149 (49.2%)</b>
Median time to Relapse (in days)	59	Not Estimable	102
Hazard Ratio <sup>a</sup> (95% CI)	0.537 (0.385, 0.748)		--
P-value from logrank test <sup>b</sup>	< 0.001		--

<sup>a</sup> A hazard ratio of less than 1 indicates that aripiprazole is associated with longer times to relapse compared with the placebo.

<sup>b</sup> Based on a two-sided test against "H<sub>0</sub>: equal time-to-relapse curves" in favor of "H<sub>1</sub>: unequal time-to-relapse curves" between the two treatment groups.

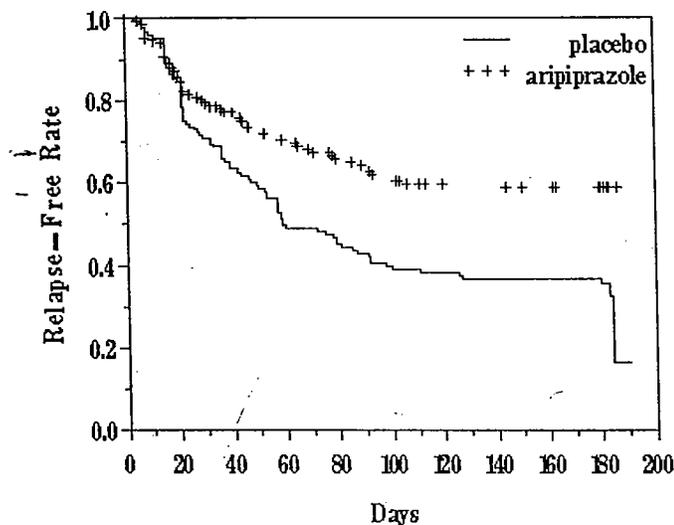
**Table 10: Reviewer's Results of Kaplan-Meier Probability of Not Experiencing Relapse (Reviewer's Efficacy Sample)**

Study Week	Probability (S.E.)	
	Placebo	Aripiprazole
2	0.9533 (0.0172)	0.9399 (0.0194)
4	0.7148 (0.0372)	0.8084 (0.0326)
6	0.6222 (0.0403)	0.7715 (0.0351)
10	0.4896 (0.0421)	0.6808 (0.0395)
18	0.3757 (0.0414)	0.5967 (0.0420)
26	0.3574 (0.0414)	0.5886 (0.0422)

S.E.: standard error of the estimated probability.

Figure 2: Reviewer's Kaplan-Meier Plot of Time-to-Relapse (Reviewer's Efficacy Sample)

Time from Randomization to Relapse (Reviewer Efficacy Sample)



### 3.1.7.6 Analysis of Number of Relapses (Secondary Endpoint)

#### 3.1.7.6.1 Sponsor's Results

The number of relapses was not clearly defined in the protocol. Based on the sponsor's Study Report, it meant the number of patients who experienced relapse before patient discontinuation of the study. The sponsor calculated the relative risk (i.e., ratio of relapse rates) based on the CMH test statistic adjusted for study center as summarized in Table 11. Also included in this table are the breakdown of the criteria (reasons) based on which a relapse was determined. Some patients experienced relapse based on more than one criterion. The relative risk (aripiprazole / placebo) was estimated to be 0.585 by the sponsor, implying that the relapse rate in the aripiprazole group was estimated to be 58.5% of that in the placebo group by the end of the study. The corresponding p-value was less than 0.001. Based on these results, the sponsor concluded that there were statistically significantly more relapses in the placebo group than in the aripiprazole group.

**Table 11: Sponsor's Summary of Reasons for Relapse and Number of Relapses (Sponsor's Efficacy Sample)**

Reason <sup>a</sup>	Number of Patients (%)	
	Placebo N = 149	Aripiprazole N = 148
CGI Improvement Score $\geq$ 5	72 (48.3)	41 (27.2)
PANSS Score $\geq$ 5 on Items of Hostility or Uncooperativeness on 2 Successive Days	14 (9.4)	7 (4.7)
$\geq$ 20% Increase in PANSS Total Score	42 (28.2)	29 (19.6)
Total Number of Relapses	85 (57.0)	50 (33.8)
Relative Risk (Aripiprazole:Placebo), 95% CI	0.585 (0.454, 0.755)	
P-Value <sup>b</sup>	< 0.001	

Protocol CN138-047

Source: Appendices 10.1.1, 10.1.2, 10.1.3

<sup>a</sup> Note that patients may have more than one reason for relapsing.

<sup>b</sup> CMH General Association Test controlling for treatment and study center.

### 3.1.7.6.2 Reviewer's Comments and Results

The analysis based on the CMH test statistic for comparison of relapse rates did not incorporate censoring information, so could only be exploratory. It, however, supported the conclusion of the primary analysis for the primary endpoint, time to relapse.

**The sponsor's summary of number of reasons for relapse may not be meaningful.** As noted by this reviewer, based on the sponsor's Study Report the number of relapses actually meant the number of patients who experienced relapse before **patient discontinuation of the study**. This implied that a patient who experienced relapse on a given day based on one criterion could be determined having relapsed based on another criterion on a later day before this patient discontinued the study. In that event, the patient was determined having relapsed based on more than one criterion (reason) by the sponsor although these criteria were not met on the same day. Although it was expected for patients to be immediately withdrawn from the study after experiencing relapse, not every patient was immediately withdrawn. As summarized in Table 12, 78% and 72% of patients, respectively, who experienced relapse discontinued the study on the date of relapse; 7% and 8% of patients, respectively, continued the study for more than a week since relapse.

**Table 12: Reviewer’s Summary of Proportions of Patients Who Discontinued The 26-Week Study after Relapse (Reviewer’s Efficacy Sample)**

Dropout date	Placebo N = 92	Aripiprazole N = 57
Before the day of relapse <sup>a</sup>	0	1
On the day of relapse	72/92 (78%)	41/57 (72%)
Within a week since relapse	14/92 (15%)	11/57 (19%)
More than a week since relapse <sup>b</sup>	6/92 (7%)	4/57 (8%)

<sup>a</sup> This could be a data key-in error from the sponsor.

<sup>b</sup> Duration ranged from 8 to 135.

It is to be noted that analysis of time-to-relapse depended on the earliest date when relapse was determined and the criteria (reasons) that were met afterwards would not have any influence on the analysis of time-to-relapse. This reviewer obtained a summary of reasons for relapse by only including criteria met on the earliest date of relapse as in Table 13. The most common criteria by which patients were determined to have relapsed were (1) “CGI Improvement Score  $\geq 5$ ” alone [51/92 = 55.4% and 28/57 = 49.1%, respectively] and (2) simultaneous “CGI Improvement Score  $\geq 5$ ” and “ $\geq 20\%$  Increase in PANSS Total Score” [24/92 = 26.1% and 19/57 = 33.3%, respectively]. The reason for “CGI-I Score  $\geq 5$ ” being the criterion most frequently associated with relapse might be due to the fact that the schedule for the CGI rating was more intensive than that for the PANSS rating – the former was rated twice as frequently as the latter (ref. Section 3.1.4.1).

There were only 2 patients in each treatment group for whom relapse was solely based on the criterion “Hostility/ Uncooperativeness PANSS Score  $\geq 5$ ”. In addition, there was no recorded score for the following day for these patients. [ ]

**Table 13: Reviewer’s Summary of Reasons for Relapse (Reviewer’s Efficacy Sample)**

Criteria (Reasons)	Number of Patients Who Relapsed		
	Placebo N = 92	Aripiprazole N = 57	Combined N = 149
CGI Improvement Score $\geq 5$ Alone	51 (55.4%)	28 (49.1%)	79 (53.0%)
PANSS Score $\geq 5$ on Hostility or Uncooperativeness Alone	2	2	4
$\geq 20\%$ Increase in PANSS Total Score Alone	3	2	5
Simultaneous CGI Improvement Score $\geq 5$ AND Hostility/Uncooperativeness PANSS Score $\geq 5$	7	2	9
Simultaneous CGI Improvement Score $\geq 5$ AND $\geq 20\%$ Increase in PANSS Total Score	24 (26.1%)	19 (33.3%)	43 (28.9%)
Simultaneous Hostility/Uncooperativeness PANSS Score $\geq 5$ AND $\geq 20\%$ Increase in PANSS Total Score	0	1	1
All of the three reasons simultaneously	5	3	8

### 3.2 EVALUATION OF SAFETY

Not reviewed by this reviewer.

## 4 FINDINGS IN SPECIAL/SUBGROUP POPULATION

Code of Federal Regulations (21 CFR 314.50) requires that efficacy data be presented by gender, age, and racial subgroups when applying for FDA approval to market a new drug. Included in this Section are this reviewer's exploratory subgroup analyses by these demographic factors as well as some other important factors.

### 4.1 GENDER

There were higher proportions of patients who experienced relapse in the placebo group in each gender. The exploratory analysis did not suggest any inconsistent results between male and female subgroups.

**Table 14: Reviewer's Summary of Time-to-Relapse by Gender (Reviewer's Efficacy Sample)**

Subgroup: Sex		Placebo (N = 152)	Aripiprazole (N = 151)	Combined (N = 303)
Male	# of patients	88	81	169
	# of Patients Who Relapsed	53 (60.2%)	32 (39.5%)	85 (50.3%)
	Median Time to Relapse (days)	57	Not Estimable	102
Female	# of patients	64	70	134
	# of Patients Who Relapsed	39 (60.9%)	25 (35.7%)	64 (47.8%)
	Median Time to Relapse (days)	60	Not Estimable	102

## 4.2 RACE

There were 274 patients (90.4% of the Efficacy Sample) in Caucasians subgroup and only 29 patients in the non-Caucasian subgroup. Since very few patients were in the non-Caucasian subgroup, the subgroup analysis by race was not informative.

**Table 15: Reviewer's Summary of Time-to-Relapse by Race (Reviewer's Efficacy Sample)**

Subgroup: Race		Placebo (N = 152)	Aripiprazole (N = 151)	Combined (N = 303)
Caucasian	# of patients	138	136	274
	# of Patients Who Relapsed	85 (61.6%)	45 (36.0%)	130
	Median Time to Relapse (days)	58	Not Estimable	106
Non-Caucasian	# of patients	14	15	29
	# of Patients Who Relapsed	7 (50%)	8 (53.3%)	15
	Median Time to Relapse (days)	126	29	91

## 4.3 AGE

There were higher proportions of patients who experienced relapse in the placebo group in each age subgroup. The exploratory analysis did not suggest any inconsistent results between age subgroups.

**Table 16: Reviewer's Summary of Time-to-Relapse by Age Group (Reviewer's Efficacy Sample)**

Subgroup: Age		Placebo (N = 152)	Aripiprazole (N = 151)	Combined (N = 303)
< 50	# of patients	109	109	218
	# of Patients Who Relapsed	67 (61.5%)	39 (35.8%)	106
	Median Time to Relapse (days)	58	Not Estimable	102
≥ 50	# of patients	43	42	85
	# of Patients Who Relapsed	25 (58.1%)	18 (42.8%)	43
	Median Time to Relapse (days)	92	Not Estimable	102

#### 4.4 OTHER SPECIAL/SUBGROUP POPULATIONS

**Country:** There were consistently higher proportions of patients who had relapse in the placebo group in each country. The results did not suggest inconsistency among countries.

**Table 17: Reviewer's Summary of Time-to-Relapse by Country (Reviewer's Efficacy Sample)**

Subgroup: Country		Placebo (N = 152)	Aripiprazole (N = 151)	Combined (N = 303)
U.S.A.	# of patients	27	28	55
	# of Patients Who Relapsed	16 (59.3%)	13 (46.4%)	29
	Median Time to Relapse (days)	92	71	91
Czech Republic	# of patients	7	7	14
	# of Patients Who Relapsed	4 (57.1%)	3 (42.9%)	7
	Median Time to Relapse (days)	42	Not Estimable	Not Estimable
Ukraine	# of patients	18	19	37
	# of Patients Who Relapsed	12 (66.7%)	7 (36.8%)	19
	Median Time to Relapse (days)	58	Not Estimable	127
Poland	# of patients	24	24	48
	# of Patients Who Relapsed	16 (66.7%)	12 (50.0%)	28
	Median Time to Relapse (days)	58	102	87
Russia	# of patients	76	73	149
	# of Patients Who Relapsed	44 (57.9%)	22 (30.1%)	66
	Median Time to Relapse (days)	59	Not Estimable	Not Estimable

**Baseline CGI-I Score:** There were higher proportions of patients who had relapse in the placebo group in each baseline CGI-I score subgroup. The results did not suggest inconsistency between subgroups.

**Table 18: Reviewer's Summary of Time-to-Relapse by Baseline CGI-S Score (Reviewer's Efficacy Sample)**

Subgroup: Baseline CGI-S Score		Placebo (N = 152)	Aripiprazole (N = 151)	Combined (N = 303)
≤ 3	# of patients	68	79	147
	# of Patients Who Relapsed	37 (54.4%)	23 (29.1%)	60
	Median Time to Relapse (days)	58	Not Estimable	Not Estimable
≥ 4	# of patients	84	72	156
	# of Patients Who Relapsed	55 (65.5%)	34 (47.2%)	89
	Median Time to Relapse (days)	59	89	78

## 5 SUMMARY AND CONCLUSIONS

### 5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

#### 5.1.1 *Statistical Issues*

- [1] **Lack of Confirmation for Patients Who Relapsed Due to PANSS score  $\geq 5$  on the Item of Hostility or Uncooperativeness:** Relapse based on reaching PANSS score  $\geq 5$  on the item of hostility or uncooperativeness required maintenance of the score on two successive days. This reviewer noted that for patients who had a score  $\geq 5$  on either of these two items on a given day, there was no recorded score for the following day. Nonetheless, the sponsor considered these patients as relapsing on the first day of such a score without meeting the formal criteria. There were only 2 patients in each arm who relapsed solely based on this criterion (but without the following day confirmation). [ ]
- [2] **Different Schedules for CGI-I and PANSS Score Ratings:** Per protocol, the CGI-I scores were rated twice as frequently as the PANSS scores (both were rated at the end of weeks 3, 6, 10, 18 and 26; in addition, CGI-I scores were also rated at the end of weeks 1, 2, 4, 8, 14 and 22). Although patients were clinically supervised daily to assess possible worsening of symptoms and the need for an unscheduled evaluation, the CGI-I being the most common criterion for relapse could be explained by its more intensive rating schedule.
- [3] **Other issues included**
- inconsistency in calculation of time-to-relapse between the definition (from the randomization date) and what was actually calculated in the sponsor's study report (from the first dose date),
  - recording errors in relapse date in the sponsor's data set,
  - inconsistency in efficacy sample between the definition and what was actually used (a difference of 6 patients),
  - inappropriate summary of reasons for relapse by sponsor, because all the criteria met before a patient discontinued the study were included in the sponsor's summary but not every patient was immediately withdrawn from the study after relapse.

#### 5.1.2 *Collective Evidence*

Time to relapse was the primary endpoint in this 26-week study. A total of 303 patients (152 in the placebo and 151 in the aripiprazole groups) were included in this reviewer's Efficacy Sample. A total of 149 patients (92 in the placebo and 57 in the aripiprazole groups) relapsed by the end of the study. The p-value from the logrank test was less than 0.001 and the estimated hazard ratio (aripiprazole/placebo) was 0.537 with a 95% confidence interval of (0.385, 0.748). This indicated that patients in the aripiprazole group were associated with longer times to relapse as compared with the placebo group. Under the assumption of a constant hazard ratio, the instantaneous risk for an aripiprazole patient to relapse was estimated to be 50.3% of that for a placebo patient given that the patient had not yet relapsed. The Kaplan-Meier probabilities of not

experiencing relapse by week 26 were estimated to be 35.7% for the placebo group and 58.9% for the aripiprazole groups.

There were no inconsistent findings between subgroups. Although several issues were noted by this reviewer, the overall conclusion was consistent between this reviewer's and the sponsor's that the aripiprazole group was associated with longer times to relapse compared to the placebo group.

Very few patients who experienced based on the criterion of PANSS score  $\geq 5$  on the item of hostility or uncooperativeness. In addition, there was no recorded score by this criterion for these patients for the following day as required for confirmation. There were only 2 patients in each treatment group who relapsed solely based on this criterion. [ ]

## 5.2 CONCLUSIONS AND RECOMMENDATIONS

There was statistically significant evidence that aripiprazole was associated with longer times to relapse. Three criteria (CGI-I score  $\geq 5$ , PANSS score  $\geq 5$  on the item of hostility or uncooperativeness on 2 successive days,  $\geq 20\%$  increase in PANSS total scores) were used in defining relapse. It was noted, however, relapse was rarely based on the criterion of PANSS score  $\geq 5$  on hostility or uncooperativeness. In addition, for those who relapsed by this criterion, there was no recorded score for the following day as required for confirmation. [ ]

## 6 APPENDICES

None.

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

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Peiling Yang  
7/29/03 10:53:06 AM  
BIOMETRICS

Kun Jin  
7/29/03 02:54:17 PM  
BIOMETRICS

George Chi  
7/29/03 03:03:46 PM  
BIOMETRICS

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 21-436/S-001**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

# Patent Information

pursuant to 21 C.F.R. §314.53  
for

**ABILIFY™ (aripiprazole) Tablets**

**sNDA for Relapse Prevention**

**(NDA 21-436)**

---

Patent No.:	U.S. 4,734,416
Patent Expiration:	March 29, 2005
Patent Type:	Drug and Method of Use
Patent Owner:	Otsuka Pharmaceutical Co., Ltd., of Tokyo, Japan
NDA Applicant:	Otsuka Pharmaceutical Co., Ltd.
NDA Applicant's Agent (Representative):	Otsuka Maryland Research Institute, Inc.
Active ingredient:	Aripiprazole
Formulation:	Tablet
Strength:	2 mg, 5 mg, 10 mg, 15 mg, 20 mg and 30 mg

The undersigned declares that Patent No. U.S. 4,734,416 covers the formulation, composition and/or method of use of ABILIFY™ (aripiprazole) Tablets. This product is the subject of this supplementary new drug application under NDA 21-436 for which approval is being sought.

Patent No.: U.S. 5,006,528  
Patent Expiration: October 20, 2009  
Patent Type: Drug and Method of Use  
Patent Owner: Otsuka Pharmaceutical Co., Ltd., of Tokyo, Japan  
NDA Applicant: Otsuka Pharmaceutical Co., Ltd.  
NDA Applicant's Agent (Representative): Otsuka Maryland Research Institute, Inc.  
Active ingredient: Aripiprazole  
Formulation: Tablet  
Strength: 2 mg, 5 mg, 10 mg, 15 mg, 20 mg and 30 mg

The undersigned declares that Patent No. U.S. 5,006,528 covers the formulation, composition and/or method of use of ABILIFY™ (aripiprazole) Tablets. This product is the subject of this supplementary new drug application under NDA 21-436 for which approval is being sought.

Please address all communications to:

Otsuka Maryland Research Institute, Inc.  
2440 Research Blvd.  
Rockville, MD 20850  
Attn: Sheila A. Cleary, Legal Affairs

Respectfully submitted,

11/21/02

Date

Sheila A. Cleary

Sheila A. Cleary, Esq.  
Attorney for Applicant

EXCLUSIVITY SUMMARY for NDA # 21-436 SUPPL # 001

Trade Name Abilify Generic Name aripiprazole

Applicant Name BMS / Otsuka HFD- 120

Approval Date 8/28/03

**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/\_\_\_/ NO / no /

b) Is it an effectiveness supplement? YES / yes / NO ~~✓~~ \_\_\_ /

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

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?

three

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 / yes / NO / \_\_\_ /

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

NDA # 21-436

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 / 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 /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 /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 /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 # CN138-047

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 CN138-047 YES /\_\_\_/ NO /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 CN138-047      YES /\_\_\_/      NO /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 #1, Study # CN138-047  
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 # 42,776 YES / 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 / no /

If yes, explain: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

\_\_\_\_\_  
Signature of Preparer  
Title:

Date

Signature of Office or Division Director

Date

CC:  
Archival NDA  
HFD- /Division File  
HFD- /RPM  
HFD-610/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

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/s/

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Steve Hardeman  
8/28/03 02:28:10 PM

**PEDIATRIC PAGE**

(Complete for all APPROVED original applications and efficacy supplements)

DA/BLA #: 21-436 Supplement Type (e.g. SE5): SE1 Supplement Number: S-001

Stamp Date: 12-4-02 Action Date: 8-28-03

HFD 120 Trade and generic names/dosage form: Abilify (aripiprazole) Tablets

Applicant: Bristol Myers Squibb / Otsuka Therapeutic Class: Antipsychotic

Indication(s) previously approved:

Indicated for the treatment of schizophrenia.

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: for maintaining stability in patients with schizophrenia

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply:  Partial Waiver  \*Deferred  Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

**Section A: Fully Waived Studies**

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: \_\_\_\_\_

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section B: Partially Waived Studies**

Age/weight range being partially waived:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: \_\_\_\_\_

*studies are deferred; proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section C: Deferred Studies**

Age/weight range being deferred:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. 13 Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. 17 Tanner Stage \_\_\_\_\_

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: Pediatric Written Request Issued

Date studies are due (mm/dd/yy): 2/11/08

*If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

**Section D: Completed Studies**

Age/weight range of completed studies:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Comments: \_\_\_\_\_

*If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

This page was completed by:

*{See appended electronic signature page}*

\_\_\_\_\_  
Regulatory Project Manager

cc: NDA  
HFD-950/ Terrie Crescenzi  
HFD-960/ Grace Carmouze  
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960  
301-594-7337

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/s/

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Steve Hardeman  
8/28/03 02:35:30 PM

**Request for Deferral of Submission of Data Assessing the Safety  
and Efficacy of Abilify™ (Aripiprazole) Tablets in Pediatric Patients**

Under IND #42,776 we have submitted three separate protocol outlines as proposed pediatric study requests for consideration by the Division. These studies are proposed in pediatric patients diagnosed with [redacted] [redacted].  
[redacted] [redacted]. The proposal for studies in patients with [redacted] [redacted] was provided in Submission No. 306, dated October 13, 2000 while the proposals for studies in patients with [redacted] [redacted] were included in Submission No. 391 dated October 17, 2001. Initiation of studies in pediatric patients has been delayed until a dialogue with Division has occurred in order to reach agreement on the appropriate population and study design.

Therefore, in accordance with 21CFR314.55(b), we are requesting a deferral of the requirement to provide safety and efficacy data in pediatric patients in this supplemental NDA until after the time we have had the opportunity to discuss our proposed pediatric study requests with the Division and an appropriate timeframe for provision of such data is mutually established. Studies will henceforth be conducted with due diligence and in the agreed upon timeframe.



# OTSUKA AMERICA PHARMACEUTICAL, INC.

2540 Research Boulevard, Rockville, Maryland 20850  
Telephone (301) 990-0030 Telefax (301) 990-0017

## CERTIFICATION: DEBARRED PERSONS

Otsuka America Pharmaceutical certifies that to the best of its knowledge, information, and belief, it has not used and will not use the services of any person listed as debarred as of May 7, 2002 Debarment List under Section 306 (a) or (b) of the Federal Food and Drug Cosmetic Act [21 U.S.C. 355 (a) or (b)] in any capacity, in connection with this Application for Aripiprazole Oral Tablets.

William H. Carson, M.D.

William Carson, M.D.  
Vice President, Product Development/Aripiprazole  
CNS Franchise  
Otsuka America Pharmaceutical  
100 Overlook Drive  
Princeton, NJ 08540  
(609) 452-2922

Division of Scientific Investigations  
Office of Medical Policy  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Rockville MD 20857

**CLINICAL INSPECTION SUMMARY**

DATE: April 9, 2003

TO: Steven D. Hardeman, R. Ph., Senior Regulatory Project Manager  
Gregory Dubitsky, M.D., Medical Officer  
Division of Neuropharmacological Drug Products, HFD-120

THROUGH: Antoine El-Hage, Ph.D., Associate Director  
Good Clinical Practice Branch I/II, HFD-46/47  
Division of Scientific Investigations

FROM: Ni A. Khin, M.D., Medical Officer  
Good Clinical Practice Branch II, HFD-47  
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspection

NDA: NDA 21-436/~~SE~~<sup>SE1</sup>-001

APPLICANT: Bristol-Myers Squibb/Otsuka

DRUG: Abilify (aripiprazole)

THERAPEUTIC CLASSIFICATION: Type S, Standard Review

INDICATION: Long Term Treatment in Schizophrenia

CONSULTATION REQUEST DATE: January 28, 2003

ACTION GOAL DATE: October 3, 2003

**I. BACKGROUND:**

Aripiprazole, a quinolone derivative, is a novel antipsychotic drug and recently, it has been approved for treatment of schizophrenia. Although the mechanism of action of aripiprazole in schizophrenia is unknown, it has been proposed that aripiprazole's efficacy is mediated through a combination of partial agonism at dopamine D<sub>2</sub> and serotonin 5-HT<sub>1A</sub> receptors and antagonism of 5-HT<sub>2</sub> receptors.

In this NDA application, the sponsor has requested the use of aripiprazole for long term treatment of schizophrenia. The application was based on results from protocol CN138-047

entitled “a multicenter, randomized, double-blind, placebo-controlled, 26-week study of a fixed dose of aripiprazole in the treatment of stabilized patients with chronic schizophrenia.” In this study, maintenance treatment with 15 mg/day of aripiprazole was given to subjects with a DSM-IV diagnosis of chronic schizophrenia over a 26-week period.

The primary objective of this study is to compare time to relapse from randomization of patients receiving 15 mg/day of aripiprazole versus placebo over 26 weeks in stabilized patients with chronic schizophrenia. Relapse is defined as one or more of the following:

- 1) CGI-improvement score of  $\geq 5$  (minimally worse)
- 2) PANSS score of  $\geq 5$  (moderately severe) on the items of hostility or uncooperativeness on 2 successive days
- 3)  $\geq 20\%$  increase in the PANSS total score.

Inspection assignment was issued on February 3, 2003 for two domestic sites, Drs. Sack and Knesevich. These investigators were the high enrollers for the study.

II. RESULTS (by site):

NAME	CITY	STATE	ASSIGNED DATE	RECEIVED DATE	CLASSIFICATION
Dr. Sack	Cerritos	CA	02-03-2003	03-24-2003	VAI
Dr. Knesevich	Dallas	TX	02-03-2003	04-03-2003	NAI

SACK, M.D.

A total of 19 subjects were screened; 4 subjects were listed as screen failures; 15 subjects were randomized and only 2 subjects (00003 and 00004) completed the 26-week study.

An audit of 8 subjects’ records was conducted. Inspectional findings included:

- 1) PI did not complete Clinical Global Impression Improvement Scores to determine relapse for seven subjects at specified study visits.  
 subject #00003, [ ] – Week 6, Week 10, Week 18, Week 26;  
 subject #00004, [ ] – Week 6, Week 10, Week 18, Week 26;  
 subject #00005, [ ] – Week 6, Week 10, early termination;  
 subject #00056, [ ] – Week 3, Early Termination;  
 subject #00058, [ ] – Week 6, Week 10, Week 18, early termination visit;  
 subject #00172, [ ] – Week 3
- 2) PI did not report immediately, as required by the protocol, to the sponsor that two subjects (#00001 and #00005) had serious adverse events; and
- 3) PI did not notify the IRB that subject 00132 experienced serious adverse event (seizure and hospitalized) during the study.

Given the finding that PI did not complete Clinical Global Impression Improvement Scores to determine “relapse” for seven subjects at specified study visits, the review division should

consider whether this issue would have any impact on the study outcome.

KNESEVICH, M.D.

A total of 17 subjects were screened; 3 subjects were listed as screen failures; 14 subjects were randomized and only 3 subjects (115, 116 and 119) completed the 26-week study. Subject 117 died from motor vehicle accident during the study. Six subjects discontinued from the study were due to exacerbation of schizophrenia (14, 118, 121, 122, 124 and 370).

An audit of all 17 subjects' records was conducted. No Form FDA-483 was issued. No major objectionable conditions noted. Overall, data appear acceptable.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

As stated above, Dr. Sack did not complete Clinical Global Impression Improvement Scores to determine "relapse" for seven subjects at specified study visits. The review division should consider excluding these seven subjects' data in efficacy data analysis. Data from Dr. Knesevich appear acceptable for use in support of this NDA.

There were no limitations to these inspections.

Key to Classifications

NAI = No deviation from regulations. Data acceptable

VAI = Minor deviation(s) from regulations. Data acceptable

VAIr = Deviation(s) from regulations, response requested. Data acceptable

OAI = Significant deviations for regulations. Data unreliable

Pending = Inspection not completed

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Ni A. Khin, M.D., Medical Officer  
Good Clinical Practice Branch II, HFD-47-  
Division of Scientific Investigations

cc:

NDA 21-436

Division File

HFD-45/Program Management Staff (electronic copy)

HFD-47/c/r/s

HFD-47/Khin/Friend

HFD-45/RF

rd: NK 04/08-04/09/03

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/s/  
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Ni Aye Khin

4/9/03 11:43:18 AM

MEDICAL OFFICER

This clinical inspection summary [DSI paper version] was initialed  
and concurred by Dr. A. El-Hage on 4/9/03.



Food and Drug Administration  
Rockville MD 20857

Mary Ann Knesevich, M.D.  
University Hills Clinical Research  
102 Decker Drive, #250  
Irving, Texas 75062

APR 18 2003

Dear Dr. Knesevich:

Between March 13 and 18, 2003, Mr. Marc R. Dickens representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (protocol CN138-047 entitled: "A multicenter, randomized, double-blind, placebo-controlled, 26-week study of a fixed dose of aripiprazole in the treatment of stabilized patients with chronic schizophrenia") of the investigational drug aripiprazole (Abilify), performed for Bristol-Myers Squibb/Otsuka Pharmaceuticals. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to monitor the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you adhered to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations.

We appreciate the cooperation shown Investigator Dickens during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

Antoine El-Hage, Ph.D.  
Associate Director  
Good Clinical Practice Branch I & II, HFD-46/47  
Division of Scientific Investigations  
Office of Medical Policy  
Center for Drug Evaluation and Research  
7520 Standish Place, Room 125  
Rockville, MD 20855

FEI: 3003915937

Field Classification: NAI

Headquarters Classification:

1)NAI

2)VAI- no response required

3)VAI- response requested

4)OAI

cc:

HFA-224

HFD-120 Doc.Rm. NDA#21-436/SE6-001

HFD-120 Review Div. Dir. Katz

HFD-120 MO Dubitsky

HFD-120 PM Hardeman

HFD-46/47c/r/s/ GCP File #10863

HFD-47 MO Khin

HFD-47 CSO Friend

HFR-SW150 DIB Thornburg

HFR-SW1540 Bimo Monitor Martinez

HFR-SW150 Field Investigator Dickens

GCF-1 Seth Ray

r/d: (NK): 4/4/03

reviewed: AEH: 4/03

f/t:ml:4/7/03

O:\NK\\_Letters\Knesevich.nai.doc

**Reviewer Note to Rev. Div. M.O.**

- For this study, subjects were seen at the facility located at St. Paul Medical Center, 5959 Harry Hines Blvd., Dallas, Texas.
- A total of 17 subjects were screened; 3 subjects were listed as screen failures; 14 subjects were randomized and only 3 subjects (115, 116 and 119) completed the 26-week study. Subject 117 died from motor vehicle accident during the study. Six subjects discontinued from the study were due to exacerbation of schizophrenia (14, 118, 121, 122, 124 and 370).
- An audit of all 17 subjects' records was conducted.
- No Form FDA-483 was issued. No major objectionable conditions noted.
- Overall, data appear acceptable.

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/s/

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Antoine El-Hage  
4/18/03 11:32:41 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

~~Needs to be logged~~  
Public Health Service

Food and Drug Administration  
Rockville MD 20857

APR 14 2003

David A. Sack, M.D.  
Comprehensive NeuroScience of Southern California, LLC  
11050 E. Artesia Blvd., Suite G  
Cerritos, California 90703

Dear Dr. Sack:

Between February 20 and 26, 2003, Ms. Tamala P. Bogan representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of a clinical investigation (protocol CN138-047 entitled "a multicenter, randomized, double-blind, placebo-controlled, 26-week study of a fixed dose of aripiprazole in the treatment of stabilized patients with chronic schizophrenia") of the investigational drug aripiprazole (Abilify), performed for Bristol-Myers Squibb/Otsuka Pharmaceuticals. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to monitor the conduct of research and to ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

From our review of the establishment inspection report and the documents submitted with that report, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations. We are aware that at the conclusion of the inspection, Ms. Bogan presented and discussed with you Form FDA 483, Inspectional Observations. We acknowledge receipt of your letter dated March 13, 2003 and wish to emphasize the following:

1. You did not adhere to the protocol in that Clinical Global Impression (CGI) Improvement rating assessment were not performed at specified study visits to determine relapse for seven subjects (00003, 00004, 00005, 00056, 00058 and 00172) (21 CFR 312.60).
2. You did not promptly report serious adverse events experienced by two subjects (00001 and 00005) to the sponsor (21 CFR 312.64).
3. You did not notify the IRB that subject 00132 experienced serious adverse event (seizure and hospitalization) during the study (21 CFR 312.66).

We note your response that you have instituted corrective procedures to ensure that the findings noted above are not repeated in any ongoing or future studies. Any response and all correspondence will be included as a permanent part of your file.

We appreciate the cooperation shown Investigator Bogan during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely,

A handwritten signature in cursive script that reads "Antoine El-Hage". The signature is written in black ink and is positioned above the typed name and address.

Antoine El-Hage, Ph.D.  
Associate Director  
Good Clinical Practice Branch I & II, HFD-46/47  
Division of Scientific Investigations  
Office of Medical Policy  
Center for Drug Evaluation and Research  
7520 Standish Place, Room 125  
Rockville, MD 20855

FEI: 3003915944

Field Classification: VAI

Headquarters Classification:

1)NAI

3)VAI- response received and reviewed

4)OAI

Deficiencies noted:

failure to adhere to protocol (05)

failure to notify IRB of SAE (15)

failure to report ADRS (16)

Deficiency Codes: 5, 15, 16

cc:

HFA-224

HFD-120 Doc.Rm. NDA#21-436/SE6-001

HFD-120 Review Div. Dir. Katz

HFD-120 MO Dubitsky

HFD-120 PM Hardeman

HFD-46/47c/r/s/ GCP File #10858

HFD-47 NK/BF

HFR-PA252 DIB Tucker

HFR-PA2565 Bimo Monitor Koller

HFR-PA200 Field Investigator Bogan

GCF-1 Seth Ray

r/d: (NK): 4/1/03

reviewed: AEH: 4/3/03

f/t:ml:4/7/03

O:\NK\ Letters\Sack.vairr.doc

**Reviewer Note to Rev. Div. M.O.**

- For this study, subjects were seen at the facility located at 10802 College Place, Cerritos, CA. A total of 19 subjects were screened; 4 subjects were listed as screen failures; 15 subjects were randomized and only 2 subjects (00003 and 00004) completed the 26-week study.
- An audit of 8 subjects' records was conducted.
- Inspectional findings included:
  - 1) PI did not complete Clinical Global Impression Improvement Scores to determine relapse for seven subjects at certain protocol specified study visits: subject #00003, JRW – Week 6, Week 10, Week 18, Week 26; subject #00004, DMB – Week 6, Week 10, Week 18, Week 26; subject #00005, ARS – Week 6, Week 10, early termination; subject #00056, MFS – Week 3, Early Termination; subject #00058, RJS – Week 6, Week 10, Week 18, early termination visit; subject #00172, KBW – Week 3;
  - 2) PI did not report immediately, as required by the protocol, to the contract research organization/the sponsor that two subjects (#00001 and #00005) had serious adverse events;
  - 3) PI did not notify the IRB that subject 00132 experienced serious adverse event (seizure and hospitalized) during the study.
- Given the finding that PI did not complete Clinical Global Impression Improvement Scores to determine "relapse" for seven subjects at specified study visits as stated above, the review division should consider whether this issue would have any impact on the study outcome.

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/s/

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Antoine El-Hage  
5/6/03 06:58:12 AM

# NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

## Applicant Information

NDA 21-436	Efficacy Supplement Type SE1	Supplement Number 001
Drug: Abilify (aripiprazole)		Applicant: Bristol Myers Squibb / Otsuka
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):
<b>❖ Application Classifications:</b>		
• Review priority		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
• Chem class (NDAs only)		
• Other (e.g., orphan, OTC)		N/A
<b>❖ User Fee Goal Dates</b>		10/4/03
<b>❖ Special programs (indicate all that apply)</b>		<input checked="" type="checkbox"/> None 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
<b>❖ User Fee Information</b>		
• 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
<b>❖ Application Integrity Policy (AIP)</b>		
• 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
<b>❖ 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.</b>		<input checked="" type="checkbox"/> Verified
<b>❖ Patent</b>		
• 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)(i)(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
<b>❖ Exclusivity Summary (approvals only)</b>		Done
<b>❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)</b>		N/A

Continued 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)	Attached to AP letter
• Most recent applicant-proposed labeling	In package
• 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)	none
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	none
Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	n/a
• Applicant proposed	n/a
• Reviews	n/a
❖ 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)	n/a
• 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

**Clinical and Summary Information**

❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	n/a
❖ Clinical review(s) (indicate date for each review)	7/10/03
❖ Microbiology (efficacy) review(s) (indicate date for each review)	n/a
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	n/a
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	In package
❖ Statistical review(s) (indicate date for each review)	7/29/03
❖ Biopharmaceutical review(s) (indicate date for each review)	n/a
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	n/a
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	4/9/03
• Bioequivalence studies	n/a

**CMC Information**

❖ CMC review(s) (indicate date for each review)	n/a this section
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	
• 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)	
❖ Facilities inspection (provide EER report)	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ Methods validation	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested

**Nonclinical Pharm/Tox Information**

❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	n/a this section
❖ Nonclinical inspection review summary	
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	
❖ CAC/ECAC report	

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

-----  
Steve Hardeman  
8/28/03 02:32:32 PM

**Hardeman, Steven D**

---

**From:** Hardeman, Steven D  
**Sent:** Thursday, August 28, 2003 11:21 AM  
**To:** 'Charles D Wolleben'  
**Subject:** RE: aripiprazole labeling

Chuck,

Dr. Laughren is OK with active controlled.

I will forward the package to Dr. Katz with the following text: . . . **in a long-term (52-week) active controlled study.** . . .

Steve

-----Original Message-----

**From:** Charles D Wolleben [mailto:Charles.Wolleben@bms.com]  
**Sent:** Thursday, August 28, 2003 11:08 AM  
**To:** Hardeman, Steven D  
**Subject:** Re: aripiprazole labeling

How about "active controlled" vs  ?

Charles D Wolleben wrote:

Steve:

This study, 217/304, was a blinded, haloperidol controlled study. Therefore is   really the term we want to move forward with? I am certain folks on this end will have this reaction.

Chuck

"Hardeman, Steven D" wrote:

Chuck, Drs. Laughren and Dubitsky are OK with your addition. However they want to add that the 52 week study was   Once I get your nod, I will give Dr. Katz the package. Steve-----Original Message-----

**From:** Charles D Wolleben [mailto:Charles.Wolleben@bms.com]  
**Sent:** Wednesday, August 27, 2003 3:57 PM  
**To:** Hardeman, Steven D  
**Cc:** Mallikaarjun, Kusuma  
**Subject:** Re: aripiprazole labeling

Steve:

Thanks for the note. I have reviewed these revisions with the team on this end and we have no problem with the changes on pgs. 8

and 29. Regarding the change on pg. 24, we acknowledge the discrepancy between the incidence of tremor in this study vs the short term studies. However, we feel that it is important to place this finding in context so as not to mislead the practitioner with regard to the nature of tremor observed. As a result, we have proposed some language that offers some details regarding this finding. We would propose the following revision (in red) to the Division's proposal:

"The adverse events reported in a 26-week, double-blind trial comparing ABILIFY and placebo were generally consistent with those reported in the short-term, placebo-controlled trials, except for a higher incidence of tremor [9% (13/153) for ABILIFY vs. 1% (2/153) for placebo]. In this study, the majority of the cases of tremor were of mild intensity (9/13 mild and 4/13 moderate), occurred early in therapy (9/13 ≤49 days) and were of limited duration (9/13 ≤10 days). Tremor infrequently led to discontinuation (<1%) of ABILIFY. In addition, in a long-term [ ] (52-week) study, the incidence of tremor for ABILIFY was 4% (34/859)."

The complete word version of the labeling which includes this highlighted proposal is attached FYI.

We look forward to feedback on this proposal and moving this supplement to an action letter. Give me a call if there are questions.

Chuck

"Hardeman, Steven D" wrote:

"WorldSecure <wmghpwwsecp01.hpw.stf.bms.com>" made the following annotations on 08/27/03 07:12:57

[INFO] -- Access Manager:  
This message was sent from CDER in an encrypted format, and decrtped by BMS mail servers.

=====

Chuck,

We reviewed your responses to Dr. Katz' questions and made some changes to the labeling (pages 8,24,29).

Page 8 and 29: added "..., were discontinued

from those other medications, ..."  
Page 24: added ". . . , except for a higher  
incidence of tremor (9% for ABILIFY vs. 1% for  
placebo)."

Let me know and I will get the package back to  
Dr. Katz.

Steve

<<Division Labeling Proposal 8-27-03.doc>>

\*\*\*\*\*

**CAPT Steven D. Hardeman, R.Ph.**  
Senior Regulatory Project Manager  
Division of Neuropharmacological Drug Products / HFD-  
120  
Food and Drug Administration  
Rockville, Maryland 20857

Phone: 301-594-5525  
Fax: 301-594-2859  
Email: [hardemans@cdcr.fda.gov](mailto:hardemans@cdcr.fda.gov)

"MMS <[cdcr.fda.gov](mailto:cdcr.fda.gov)>" made the following annotations.

---

This message was sent from Bristol-Myers Squibb, Co. across the  
Internet in encrypted format and was successfully decrypted,  
unless otherwise noted. Bristol-Myers Squibb

---

"WorldSecure <[wmghpwwsecp01.hpw.stf.bms.com](mailto:wmghpwwsecp01.hpw.stf.bms.com)>" made the  
following  
annotations on 08/28/03 10:32:14

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[INFO] -- Access Manager:  
This message was sent from CDER in an encrypted format, and was  
decrtped by BMS mail servers.

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"MMS <[cdcr.fda.gov](mailto:cdcr.fda.gov)>" made the following annotations.

---

This message was sent from Bristol-Myers Squibb, Co. across the Internet in encrypted format  
and was successfully decrypted, unless otherwise noted. Bristol-Myers Squibb

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Laughren, Thomas P

---

From: Laughren, Thomas P  
Sent: Tuesday, August 26, 2003 3:53 PM  
To: Hardeman, Steven D  
Subject: Aripiprazole Labeling

Steve,

\ Rather than making the changes on the electronic document, I have given them to you in hardcopy (on your desk). They are minor. I have discussed them with Greg, and he is in agreement.

Thanks,

Tom

that trial. ABILIFY was only significantly different compared to placebo in a responder analysis based on the CGI-severity score.

Thus, the efficacy of 15-mg, 20-mg, and 30-mg daily doses was established in two studies for each dose, whereas the efficacy of the 10-mg dose was established in one study. There was no evidence in any study that the higher dose groups offered any advantage over the lowest dose group.

An examination of population subgroups did not reveal any clear evidence of differential responsiveness on the basis of age, gender, or race.

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A longer-term trial enrolled 310 inpatients or outpatients meeting DSM-IV criteria for schizophrenia who were, by history, symptomatically stable on other antipsychotic medications for periods of 3 months or longer. These patients were discontinued from their antipsychotic medications and randomized to ABILIFY 15 mg or placebo for up to 26 weeks of observation for relapse. Relapse during the double-blind phase was defined as CGI-Improvement score of  $\geq 5$  (minimally worse), scores  $\geq 5$  (moderately severe) on the hostility or uncooperativeness items of the PANSS, or  $\geq 20\%$  increase in the PANSS Total score. Patients receiving ABILIFY 15 mg experienced a significantly longer time to relapse over the subsequent 26 weeks compared to those receiving placebo.

## INDICATIONS AND USAGE

ABILIFY is indicated for the treatment of schizophrenia. The efficacy of ABILIFY in the treatment of schizophrenia was established in short-term (4- and 6-week) controlled trials of schizophrenic inpatients (see **CLINICAL PHARMACOLOGY: Clinical Studies**).

The efficacy of ABILIFY in maintaining stability in patients with schizophrenia who had been symptomatically stable on other antipsychotic medications for periods of 3 months or longer and were then administered ABILIFY 15 mg/day and observed for relapse during a period of up to 26 weeks was demonstrated in a placebo-controlled trial (see **CLINICAL PHARMACOLOGY: Clinical Studies**). The physician who elects to use ABILIFY for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see **DOSAGE AND ADMINISTRATION**).

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were discontinued from those other medications

aripiprazole dose should be doubled (to 20 or 30 mg). Additional dose increases should be based on clinical evaluation. When carbamazepine is withdrawn from the combination therapy, the aripiprazole dose should be reduced to 10 to 15 mg.

### Maintenance Therapy

*were discontinued from these medications*

While there is no body of evidence available to answer the question of how long a patient treated with aripiprazole should remain on it, systematic evaluation of patients with schizophrenia who had been symptomatically stable on other antipsychotic medications for periods of 3 months or longer and were then administered ABILIFY 15 mg/day and observed for relapse during a period of up to 26 weeks demonstrated a benefit of such maintenance treatment (see CLINICAL PHARMACOLOGY: Clinical Studies). Patients should be periodically reassessed to determine the need for maintenance treatment.

- Deleted: There
- Deleted: from controlled trials
- Deleted: . It is generally agreed, however, that pharmacological treatment for episodes
- Deleted: acute
- Deleted: should continue for up to 6
- Deleted: .
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### Switching from Other Antipsychotics

There are no systematically collected data to specifically address switching patients with schizophrenia from other antipsychotics to ABILIFY or concerning concomitant administration with other antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some patients with schizophrenia, more gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized.

### ANIMAL TOXICOLOGY

Aripiprazole produced retinal degeneration in albino rats in a 26-week chronic toxicity study at a dose of 60 mg/kg and in a 2-year carcinogenicity study at doses of 40 and 60 mg/kg. The 40- and 60-mg/kg doses are 13 and 19 times the maximum recommended human dose (MRHD) based on mg/m<sup>2</sup> and 7 to 14 times human exposure at MRHD based on AUC. Evaluation of the retinas of albino mice and of monkeys did not reveal evidence of retinal degeneration. Additional studies to further evaluate the mechanism have not been performed. The relevance of this finding to human risk is unknown.

### HOW SUPPLIED

ABILIFY™ (aripiprazole) Tablets are available in the following strengths and packages.

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30 mg/day, aripiprazole tended to slightly shorten the QTc interval. Aripiprazole was associated with a median increase in heart rate of 4 beats per minute compared to a 1 beat per minute increase among placebo patients.

### Additional Findings Observed in Clinical Trials

#### Adverse Events in a Long-Term, Double-Blind, Placebo-Controlled Trial

The adverse events reported in a 26-week, double-blind trial comparing ABILIFY and placebo were generally consistent with those reported in the short-term, placebo-controlled trials. except for a higher incidence of tremor

(9% for ABILIFY vs 1% for placebo)

#### **Other Adverse Events Observed During the Premarketing Evaluation of Aripiprazole**

Following is a list of modified COSTART terms that reflect treatment-emergent adverse events as defined in the introduction to the ADVERSE REACTIONS section reported by patients treated with aripiprazole at multiple doses  $\geq 2$  mg/day during any phase of a trial within the database of 5592 patients. All reported events are included except those already listed in Table 1, or other parts of the ADVERSE REACTIONS section, those considered in the WARNINGS or PRECAUTIONS, those event terms which were so general as to be uninformative, events reported with an incidence of  $<0.05\%$  and which did not have a substantial probability of being acutely life-threatening, events that are otherwise common as background events, and events considered unlikely to be drug related. It is important to emphasize that, although the events reported occurred during treatment with aripiprazole, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

*Body as a Whole: Frequent* - flu syndrome, peripheral edema, chest pain, neck pain, neck rigidity; *Infrequent* - pelvic pain, suicide attempt, face edema, malaise, photosensitivity, arm rigidity, jaw pain, chills, bloating, jaw tightness, enlarged abdomen,

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8, 24, 29

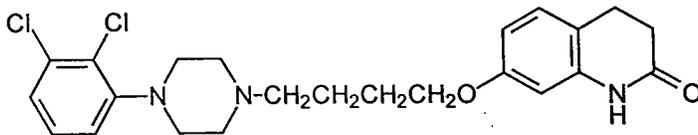
Last Approved vs. Agreed

**ABILIFY™**  
(aripiprazole) Tablets

**Rx only**

**DESCRIPTION**

ABILIFY™ (aripiprazole) is a psychotropic drug that is available as tablets for oral administration. Aripiprazole is 7-[4-[4-(2,3-dichlorophenyl)-1-piperaziny]butoxy]-3,4-dihydrocarbostyryl. The empirical formula is  $C_{23}H_{27}Cl_2N_3O_2$  and its molecular weight is 448.38. The chemical structure is:



ABILIFY tablets are available in 5-mg, 10-mg, 15-mg, 20-mg, and 30-mg strengths. Inactive ingredients include lactose monohydrate, cornstarch, microcrystalline cellulose, hydroxypropyl cellulose, and magnesium stearate. Colorants include ferric oxide (yellow or red) and FD&C Blue No. 2 Aluminum Lake.

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**CLINICAL PHARMACOLOGY**

**Pharmacodynamics**

Aripiprazole exhibits high affinity for dopamine  $D_2$  and  $D_3$ , serotonin  $5-HT_{1A}$  and  $5-HT_{2A}$  receptors ( $K_i$  values of 0.34, 0.8, 1.7, and 3.4 nM, respectively), moderate affinity for dopamine  $D_4$ , serotonin  $5-HT_{2C}$  and  $5-HT_7$ ,  $\alpha_1$ -adrenergic and histamine  $H_1$  receptors ( $K_i$  values of 44, 15, 39, 57, and 61 nM, respectively), and moderate affinity for the serotonin reuptake site ( $K_i=98$  nM). Aripiprazole has no appreciable affinity for cholinergic muscarinic receptors ( $IC_{50}>1000$  nM). Aripiprazole functions as a partial agonist at the dopamine  $D_2$  and the serotonin  $5-HT_{1A}$  receptors, and as an antagonist at serotonin  $5-HT_{2A}$  receptor.

The mechanism of action of aripiprazole, as with other drugs having efficacy in schizophrenia, is unknown. However, it has been proposed that the efficacy of aripiprazole is mediated through a combination of partial agonist activity at  $D_2$  and  $5-HT_{1A}$  receptors and antagonist activity at  $5-HT_{2A}$  receptors. Actions at receptors other than  $D_2$ ,  $5-HT_{1A}$ , and  $5-HT_{2A}$  may explain some of the other clinical effects of

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aripiprazole, eg, the orthostatic hypotension observed with aripiprazole may be explained by its antagonist activity at adrenergic alpha<sub>1</sub> receptors.

## Pharmacokinetics

ABILIFY activity is presumably primarily due to the parent drug, aripiprazole, and to a lesser extent, to its major metabolite, dehydro-aripiprazole, which has been shown to have affinities for D<sub>2</sub> receptors similar to the parent drug and represents 40% of the parent drug exposure in plasma. The mean elimination half-lives are about 75 hours and 94 hours for aripiprazole and dehydro-aripiprazole, respectively. Steady-state concentrations are attained within 14 days of dosing for both active moieties. Aripiprazole accumulation is predictable from single-dose pharmacokinetics. At steady state, the pharmacokinetics of aripiprazole are dose-proportional. Elimination of aripiprazole is mainly through hepatic metabolism involving two P450 isozymes, CYP2D6 and CYP3A4.

## Absorption

Aripiprazole is well absorbed, with peak plasma concentrations occurring within 3 to 5 hours; the absolute oral bioavailability of the tablet formulation is 87%. ABILIFY can be administered with or without food. Administration of a 15-mg ABILIFY tablet with a standard high-fat meal did not significantly affect the C<sub>max</sub> or AUC of aripiprazole or its active metabolite, dehydro-aripiprazole, but delayed T<sub>max</sub> by 3 hours for aripiprazole and 12 hours for dehydro-aripiprazole.

## Distribution

The steady-state volume of distribution of aripiprazole following intravenous administration is high (404 L or 4.9 L/kg), indicating extensive extravascular distribution. At therapeutic concentrations, aripiprazole and its major metabolite are greater than 99% bound to serum proteins, primarily to albumin. In healthy human volunteers administered 0.5 to 30 mg/day aripiprazole for 14 days, there was dose-dependent D<sub>2</sub>-receptor occupancy indicating brain penetration of aripiprazole in humans.

## Metabolism and Elimination

Aripiprazole is metabolized primarily by three biotransformation pathways: dehydrogenation, hydroxylation, and N-dealkylation. Based on *in vitro* studies, CYP3A4

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and CYP2D6 enzymes are responsible for dehydrogenation and hydroxylation of aripiprazole, and N-dealkylation is catalyzed by CYP3A4. Aripiprazole is the predominant drug moiety in the systemic circulation. At steady state, dehydro-aripiprazole, the active metabolite, represents about 40% of aripiprazole AUC in plasma.

Approximately 8% of Caucasians lack the capacity to metabolize CYP2D6 substrates and are classified as poor metabolizers (PM), whereas the rest are extensive metabolizers (EM). PMs have about an 80% increase in aripiprazole exposure and about a 30% decrease in exposure to the active metabolite compared to EMs, resulting in about a 60% higher exposure to the total active moieties from a given dose of aripiprazole compared to EMs. Coadministration of ABILIFY with known inhibitors of CYP2D6, like quinidine in EMs, results in a 112% increase in aripiprazole plasma exposure, and dosing adjustment is needed (see **PRECAUTIONS: Drug-Drug Interactions**). The mean elimination half-lives are about 75 hours and 146 hours for aripiprazole in EMs and PMs, respectively. Aripiprazole does not inhibit or induce the CYP2D6 pathway.

Following a single oral dose of [<sup>14</sup>C]-labeled aripiprazole, approximately 25% and 55% of the administered radioactivity was recovered in the urine and feces, respectively. Less than 1% of unchanged aripiprazole was excreted in the urine and approximately 18% of the oral dose was recovered unchanged in the feces.

## Special Populations

In general, no dosage adjustment for ABILIFY is required on the basis of a patient's age, gender, race, smoking status, hepatic function, or renal function (see **DOSAGE AND ADMINISTRATION: Dosage in Special Populations**). The pharmacokinetics of aripiprazole in special populations are described below.

### Hepatic Impairment

In a single-dose study (15 mg of aripiprazole) in subjects with varying degrees of liver cirrhosis (Child-Pugh Classes A, B, and C), the AUC of aripiprazole, compared to healthy subjects, increased 31% in mild HI, increased 8% in moderate HI, and decreased 20% in severe HI. None of these differences would require dose adjustment.

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## Renal Impairment

In patients with severe renal impairment (creatinine clearance < 30 mL/min), C<sub>max</sub> of aripiprazole (given in a single dose of 15 mg) and dehydro-aripiprazole increased by 36% and 53%, respectively, but AUC was 15% lower for aripiprazole and 7% higher for dehydro-aripiprazole. Renal excretion of both unchanged aripiprazole and dehydro-aripiprazole is less than 1% of the dose. No dosage adjustment is required in subjects with renal impairment.

## Elderly

In formal single-dose pharmacokinetic studies (with aripiprazole given in a single dose of 15 mg), aripiprazole clearance was 20% lower in elderly (≥65 years) subjects compared to younger adult subjects (18 to 64 years). There was no detectable age effect, however, in the population pharmacokinetic analysis in schizophrenia patients. Also, the pharmacokinetics of aripiprazole after multiple doses in elderly patients appeared similar to that observed in young, healthy subjects. No dosage adjustment is recommended for elderly patients (see **PRECAUTIONS: Geriatric Use**).

## Gender

C<sub>max</sub> and AUC of aripiprazole and its active metabolite, dehydro-aripiprazole, are 30 to 40% higher in women than in men, and correspondingly, the apparent oral clearance of aripiprazole is lower in women. These differences, however, are largely explained by differences in body weight (25%) between men and women. No dosage adjustment is recommended based on gender.

## Race

Although no specific pharmacokinetic study was conducted to investigate the effects of race on the disposition of aripiprazole, population pharmacokinetic evaluation revealed no evidence of clinically significant race-related differences in the pharmacokinetics of aripiprazole. No dosage adjustment is recommended based on race.

## Smoking

Based on studies utilizing human liver enzymes *in vitro*, aripiprazole is not a substrate for CYP1A2 and also does not undergo direct glucuronidation. Smoking should, therefore, not have an effect on the pharmacokinetics of aripiprazole. Consistent with these *in vitro*

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results, population pharmacokinetic evaluation did not reveal any significant pharmacokinetic differences between smokers and nonsmokers. No dosage adjustment is recommended based on smoking status.

## Drug-Drug Interactions

### Potential for Other Drugs to Affect ABILIFY

Aripiprazole is not a substrate of CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2E1 enzymes. Aripiprazole also does not undergo direct glucuronidation. This suggests that an interaction of aripiprazole with inhibitors or inducers of these enzymes, or other factors, like smoking, is unlikely.

Both CYP3A4 and CYP2D6 are responsible for aripiprazole metabolism. Agents that induce CYP3A4 (eg, carbamazepine) could cause an increase in aripiprazole clearance and lower blood levels. Inhibitors of CYP3A4 (eg, ketoconazole) or CYP2D6 (eg, quinidine, fluoxetine, or paroxetine) can inhibit aripiprazole elimination and cause increased blood levels.

### Potential for ABILIFY to Affect Other Drugs

Aripiprazole is unlikely to cause clinically important pharmacokinetic interactions with drugs metabolized by cytochrome P450 enzymes. In *in vivo* studies, 10- to 30-mg/day doses of aripiprazole had no significant effect on metabolism by CYP2D6 (dextromethorphan), CYP2C9 (warfarin), CYP2C19 (omeprazole, warfarin), and CYP3A4 (dextromethorphan) substrates. Additionally, aripiprazole and dehydro-aripiprazole did not show potential for altering CYP1A2-mediated metabolism *in vitro* (see **PRECAUTIONS: Drug-Drug Interactions**).

*Aripiprazole had no clinically important interactions with the following drugs:*

*Famotidine:* Coadministration of aripiprazole (given in a single dose of 15 mg) with a 40-mg single dose of the H<sub>2</sub> antagonist famotidine, a potent gastric acid blocker, decreased the solubility of aripiprazole and, hence, its rate of absorption, reducing by 37% and 21% the C<sub>max</sub> of aripiprazole and dehydro-aripiprazole, respectively, and by 13% and 15%, respectively, the extent of absorption (AUC). No dosage adjustment of aripiprazole is required when administered concomitantly with famotidine.

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*Valproate:* When valproate (500-1500 mg/day) and aripiprazole (30 mg/day) were coadministered at steady state, the C<sub>max</sub> and AUC of aripiprazole were decreased by 25%. No dosage adjustment of aripiprazole is required when administered concomitantly with valproate.

*Lithium:* A pharmacokinetic interaction of aripiprazole with lithium is unlikely because lithium is not bound to plasma proteins, is not metabolized, and is almost entirely excreted unchanged in urine. Coadministration of therapeutic doses of lithium (1200-1800 mg/day) for 21 days with aripiprazole (30 mg/day) did not result in clinically significant changes in the pharmacokinetics of aripiprazole or its active metabolite, dehydro-aripiprazole (C<sub>max</sub> and AUC increased by less than 20%). No dosage adjustment of aripiprazole is required when administered concomitantly with lithium.

*Dextromethorphan:* Aripiprazole at doses of 10 to 30 mg per day for 14 days had no effect on dextromethorphan's O-dealkylation to its major metabolite, dextrorphan, a pathway known to be dependent on CYP2D6 activity. Aripiprazole also had no effect on dextromethorphan's N-demethylation to its metabolite 3-methoxymorphan, a pathway known to be dependent on CYP3A4 activity. No dosage adjustment of dextromethorphan is required when administered concomitantly with aripiprazole.

*Warfarin:* Aripiprazole 10 mg per day for 14 days had no effect on the pharmacokinetics of R- and S-warfarin or on the pharmacodynamic end point of International Normalized Ratio, indicating the lack of a clinically relevant effect of aripiprazole on CYP2C9 and CYP2C19 metabolism or the binding of highly protein-bound warfarin. No dosage adjustment of warfarin is required when administered concomitantly with aripiprazole.

*Omeprazole:* Aripiprazole 10 mg per day for 15 days had no effect on the pharmacokinetics of a single 20-mg dose of omeprazole, a CYP2C19 substrate, in healthy subjects. No dosage adjustment of omeprazole is required when administered concomitantly with aripiprazole.

## Clinical Studies

The efficacy of ABILIFY in the treatment of schizophrenia was evaluated in four short-term (4- and 6-week), placebo-controlled trials of acutely relapsed inpatients who predominantly met DSM-III/IV criteria for schizophrenia. Three of the four trials were able to distinguish aripiprazole from placebo, but one study, the smallest, did not. Three

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of these studies also included an active control group consisting of either risperidone (one trial) or haloperidol (two trials), but they were not designed to allow for a comparison of ABILIFY and the active comparators.

In the three positive trials for ABILIFY, four primary measures were used for assessing psychiatric signs and symptoms. The Positive and Negative Syndrome Scale (PANSS) is a multi-item inventory of general psychopathology used to evaluate the effects of drug treatment in schizophrenia. The PANSS positive subscale is a subset of items in the PANSS that rates seven positive symptoms of schizophrenia (delusions, conceptual disorganization, hallucinatory behavior, excitement, grandiosity, suspiciousness/persecution, and hostility). The PANSS negative subscale is a subset of items in the PANSS that rates seven negative symptoms of schizophrenia (blunted affect, emotional withdrawal, poor rapport, passive apathetic withdrawal, difficulty in abstract thinking, lack of spontaneity/flow of conversation, stereotyped thinking). The Clinical Global Impression (CGI) assessment reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient.

In a 4-week trial (n=414) comparing two fixed doses of ABILIFY (15 or 30 mg/day) and haloperidol (10 mg/day) to placebo, both doses of ABILIFY were superior to placebo in the PANSS total score, PANSS positive subscale, and CGI-severity score. In addition, the 15-mg dose was superior to placebo in the PANSS negative subscale.

In a 4-week trial (n=404) comparing two fixed doses of ABILIFY (20 or 30 mg/day) and risperidone (6 mg/day) to placebo, both doses of ABILIFY were superior to placebo in the PANSS total score, PANSS positive subscale, PANSS negative subscale, and CGI-severity score.

In a 6-week trial (n=420) comparing three fixed doses of ABILIFY (10, 15, or 20 mg/day) to placebo, all three doses of ABILIFY were superior to placebo in the PANSS total score, PANSS positive subscale, and the PANSS negative subscale.

In a fourth study, a 4-week trial (n=103) comparing ABILIFY in a range of 5 to 30 mg/day or haloperidol 5 to 20 mg/day to placebo, haloperidol was superior to placebo, in the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general psychopathology traditionally used to evaluate the effects of drug treatment in psychosis, and in a responder analysis based on the CGI-severity score, the primary outcomes for

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that trial. ABILIFY was only significantly different compared to placebo in a responder analysis based on the CGI-severity score.

Thus, the efficacy of 15-mg, 20-mg, and 30-mg daily doses was established in two studies for each dose, whereas the efficacy of the 10-mg dose was established in one study. There was no evidence in any study that the higher dose groups offered any advantage over the lowest dose group.

An examination of population subgroups did not reveal any clear evidence of differential responsiveness on the basis of age, gender, or race.

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A longer-term trial enrolled 310 inpatients or outpatients meeting DSM-IV criteria for schizophrenia who were, by history, symptomatically stable on other antipsychotic medications for periods of 3 months or longer. These patients were discontinued from their antipsychotic medications and randomized to ABILIFY 15 mg or placebo for up to 26 weeks of observation for relapse. Relapse during the double-blind phase was defined as CGI-Improvement score of  $\geq 5$  (minimally worse), scores  $\geq 5$  (moderately severe) on the hostility or uncooperativeness items of the PANSS, or  $\geq 20\%$  increase in the PANSS Total score. Patients receiving ABILIFY 15 mg experienced a significantly longer time to relapse over the subsequent 26 weeks compared to those receiving placebo.

## INDICATIONS AND USAGE

ABILIFY is indicated for the treatment of schizophrenia. The efficacy of ABILIFY in the treatment of schizophrenia was established in short-term (4- and 6-week) controlled trials of schizophrenic inpatients (see **CLINICAL PHARMACOLOGY: Clinical Studies**).

The efficacy of ABILIFY in maintaining stability in patients with schizophrenia who had been symptomatically stable on other antipsychotic medications for periods of 3 months or longer, were discontinued from those other medications, and were then administered ABILIFY 15 mg/day and observed for relapse during a period of up to 26 weeks was demonstrated in a placebo-controlled trial (see **CLINICAL PHARMACOLOGY: Clinical Studies**). The physician who elects to use ABILIFY for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see **DOSAGE AND ADMINISTRATION**).

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## CONTRAINDICATIONS

ABILIFY is contraindicated in patients with a known hypersensitivity to the product.

## WARNINGS

### Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including aripiprazole. Two possible cases of NMS occurred during aripiprazole treatment in the premarketing worldwide clinical database. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (eg, pneumonia, systemic infection, etc) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

### Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome

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appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and, thereby, may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, ABILIFY should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom a lternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on ABILIFY, drug discontinuation should be considered. However, some patients may require treatment with ABILIFY despite the presence of the syndrome.

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## PRECAUTIONS

### General

#### Orthostatic Hypotension

Aripiprazole may be associated with orthostatic hypotension, perhaps due to its  $\alpha_1$ -adrenergic receptor antagonism. The incidence of orthostatic hypotension associated events from five short-term, placebo-controlled trials in schizophrenia (n=926) on ABILIFY included: orthostatic hypotension (placebo 1%, aripiprazole 1.9%), orthostatic lightheadedness (placebo 1%, aripiprazole 0.9%), and syncope (placebo 1%, aripiprazole 0.6%). The incidence of a significant orthostatic change in blood pressure (defined as a decrease of at least 30 mmHg in systolic blood pressure when changing from a supine to standing position) for aripiprazole was not statistically different from placebo (14% among aripiprazole-treated patients and 12% among placebo-treated patients).

Aripiprazole should be used with caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease, or conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications).

#### Seizure

Seizures occurred in 0.1% (1/926) of aripiprazole-treated patients in short-term, placebo-controlled trials. As with other antipsychotic drugs, aripiprazole should be used cautiously in patients with a history of seizures or with conditions that lower the seizure threshold, eg, Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

#### Potential for Cognitive and Motor Impairment

In short-term, placebo-controlled trials, somnolence was reported in 11% of patients on ABILIFY compared to 8% of patients on placebo; somnolence led to discontinuation in 0.1% (1/926) of patients on ABILIFY in short-term, placebo-controlled trials. Despite the relatively modest increased incidence of somnolence compared to placebo, ABILIFY, like other antipsychotics, may have the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about operating hazardous machinery, including

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automobiles, until they are reasonably certain that therapy with ABILIFY does not affect them adversely.

### **Body Temperature Regulation**

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing aripiprazole for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, eg, exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

### **Dysphagia**

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. Aripiprazole and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia (see **PRECAUTIONS: Use in Patients with Concomitant Illness**).

### **Suicide**

The possibility of a suicide attempt is inherent in psychotic illnesses, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for ABILIFY should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

### **Use in Patients with Concomitant Illness**

*Safety Experience in Elderly Patients with Psychosis Associated with Alzheimer's Disease:* In a flexible dose (2 to 15 mg/day), 10-week, placebo-controlled study of aripiprazole in elderly patients (mean age: 81.5 years; range: 56 to 95 years) with psychosis associated with Alzheimer's dementia, 4 of 105 patients (3.8%) who received ABILIFY died compared to no deaths among 102 patients who received placebo during or within 30 days after termination of the double-blind portion of the study. Three of the patients (age 92, 91, and 87 years) died following the discontinuation of ABILIFY in the double-blind phase of the study (causes of death were pneumonia, heart failure, and shock). The fourth patient (age 78 years) died following hip surgery while in the double-blind portion of the study. The treatment-emergent adverse events that were reported at

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an incidence of  $\geq 5\%$  and having a greater incidence than placebo in this study were accidental injury, somnolence, and bronchitis. Eight percent of the ABILIFY-treated patients reported somnolence compared to one percent of placebo patients. In a small pilot, open-label, ascending-dose, cohort study (n=30) in elderly patients with dementia, ABILIFY was associated in a dose-related fashion with somnolence.

The safety and efficacy of ABILIFY in the treatment of patients with psychosis associated with dementia have not been established. If the prescriber elects to treat such patients with ABILIFY, vigilance should be exercised, particularly for the emergence of difficulty swallowing or excessive somnolence, which could predispose to accidental injury or aspiration.

Clinical experience with ABILIFY in patients with certain concomitant systemic illnesses (see **CLINICAL PHARMACOLOGY: Special Populations: Renal Impairment and Hepatic Impairment**) is limited.

ABILIFY has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies.

## Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe ABILIFY:

### Interference with Cognitive and Motor Performance

Because aripiprazole may have the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that aripiprazole therapy does not affect them adversely.

### Pregnancy

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy with ABILIFY.

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## Nursing

Patients should be advised not to breast-feed an infant if they are taking ABILIFY.

## Concomitant Medication

Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions.

## Alcohol

Patients should be advised to avoid alcohol while taking ABILIFY.

## Heat Exposure and Dehydration

Patients should be advised regarding appropriate care in avoiding overheating and dehydration.

## Drug-Drug Interactions

Given the primary CNS effects of aripiprazole, caution should be used when ABILIFY is taken in combination with other centrally acting drugs and alcohol. Due to its  $\alpha_1$ -adrenergic receptor antagonism, aripiprazole has the potential to enhance the effect of certain antihypertensive agents.

## Potential for Other Drugs to Affect ABILIFY

Aripiprazole is not a substrate of CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2E1 enzymes. Aripiprazole also does not undergo direct glucuronidation. This suggests that an interaction of aripiprazole with inhibitors or inducers of these enzymes, or other factors, like smoking, is unlikely.

Both CYP3A4 and CYP2D6 are responsible for aripiprazole metabolism. Agents that induce CYP3A4 (eg, carbamazepine) could cause an increase in aripiprazole clearance and lower blood levels. Inhibitors of CYP3A4 (eg, ketoconazole) or CYP2D6 (eg, quinidine, fluoxetine, or paroxetine) can inhibit aripiprazole elimination and cause increased blood levels.

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**Ketoconazole:** Coadministration of ketoconazole (200 mg/day for 14 days) with a 15-mg single dose of aripiprazole increased the AUC of aripiprazole and its active metabolite by 63% and 77%, respectively. The effect of a higher ketoconazole dose (400 mg/day) has not been studied. When concomitant administration of ketoconazole with aripiprazole occurs, aripiprazole dose should be reduced to one-half of its normal dose. Other strong inhibitors of CYP3A4 (itraconazole) would be expected to have similar effects and need similar dose reductions; weaker inhibitors (erythromycin, grapefruit juice) have not been studied. When the CYP3A4 inhibitor is withdrawn from the combination therapy, aripiprazole dose should then be increased.

**Quinidine:** Coadministration of a 10-mg single dose of aripiprazole with quinidine (166 mg/day for 13 days), a potent inhibitor of CYP2D6, increased the AUC of aripiprazole by 112% but decreased the AUC of its active metabolite, dehydro-aripiprazole, by 35%. Aripiprazole dose should be reduced to one-half of its normal dose when concomitant administration of quinidine with aripiprazole occurs. Other significant inhibitors of CYP2D6, such as fluoxetine or paroxetine, would be expected to have similar effects and, therefore, should be accompanied by similar dose reductions. When the CYP2D6 inhibitor is withdrawn from the combination therapy, aripiprazole dose should then be increased.

**Carbamazepine:** Coadministration of carbamazepine (200 mg BID), a potent CYP3A4 inducer, with aripiprazole (30 mg QD) resulted in an approximate 70% decrease in C<sub>max</sub> and AUC values of both aripiprazole and its active metabolite, dehydro-aripiprazole. When carbamazepine is added to aripiprazole therapy, aripiprazole dose should be doubled. Additional dose increases should be based on clinical evaluation. When carbamazepine is withdrawn from the combination therapy, aripiprazole dose should then be reduced.

No clinically significant effect of famotidine, valproate, or lithium was seen on the pharmacokinetics of aripiprazole (see **CLINICAL PHARMACOLOGY: Drug-Drug Interactions**).

#### **Potential for ABILIFY to Affect Other Drugs**

Aripiprazole is unlikely to cause clinically important pharmacokinetic interactions with drugs metabolized by cytochrome P450 enzymes. In *in vivo* studies, 10- to 30-mg/day doses of aripiprazole had no significant effect on metabolism by CYP2D6 (dextromethorphan), CYP2C9 (warfarin), CYP2C19 (omeprazole, warfarin), and

CYP3A4 (dextromethorphan) substrates. Additionally, aripiprazole and dehydro-aripiprazole did not show potential for altering CYP1A2-mediated metabolism *in vitro* (see **CLINICAL PHARMACOLOGY: Drug-Drug Interactions**).

**Alcohol:** There was no significant difference between aripiprazole coadministered with ethanol and placebo coadministered with ethanol on performance of gross motor skills or stimulus response in healthy subjects. As with most psychoactive medications, patients should be advised to avoid alcohol while taking ABILIFY.

## **Carcinogenesis, Mutagenesis, Impairment of Fertility**

### **Carcinogenesis**

Lifetime carcinogenicity studies were conducted in ICR mice and in Sprague-Dawley (SD) and F344 rats. Aripiprazole was administered for 2 years in the diet at doses of 1, 3, 10, and 30 mg/kg/day to ICR mice and 1, 3, and 10 mg/kg/day to F344 rats (0.2 to 5 and 0.3 to 3 times the maximum recommended human dose [MRHD] based on mg/m<sup>2</sup>, respectively). In addition, SD rats were dosed orally for 2 years at 10, 20, 40, and 60 mg/kg/day (3 to 19 times the MRHD based on mg/m<sup>2</sup>). Aripiprazole did not induce tumors in male mice or rats. In female mice, the incidences of pituitary gland adenomas and mammary gland adenocarcinomas and adenocanthomas were increased at dietary doses of 3 to 30 mg/kg/day (0.1 to 0.9 times human exposure at MRHD based on AUC and 0.5 to 5 times the MRHD based on mg/m<sup>2</sup>). In female rats, the incidence of mammary gland fibroadenomas was increased at a dietary dose of 10 mg/kg/day (0.1 times human exposure at MRHD based on AUC and 3 times the MRHD based on mg/m<sup>2</sup>); and the incidences of adrenocortical carcinomas and combined adrenocortical adenomas/carcinomas were increased at an oral dose of 60 mg/kg/day (14 times human exposure at MRHD based on AUC and 19 times the MRHD based on mg/m<sup>2</sup>).

Proliferative changes in the pituitary and mammary gland of rodents have been observed following chronic administration of other antipsychotic agents and are considered prolactin-mediated. Serum prolactin was not measured in the aripiprazole carcinogenicity studies. However, increases in serum prolactin levels were observed in female mice in a 13-week dietary study at the doses associated with mammary gland and pituitary tumors. Serum prolactin was not increased in female rats in 4- and 13-week dietary studies at the dose associated with mammary gland tumors. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown.

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## Mutagenesis

The mutagenic potential of aripiprazole was tested in the *in vitro* bacterial reverse-mutation assay, the *in vitro* bacterial DNA repair assay, the *in vitro* forward gene mutation assay in mouse lymphoma cells, the *in vitro* chromosomal aberration assay in Chinese hamster lung (CHL) cells, the *in vivo* micronucleus assay in mice, and the unscheduled DNA synthesis assay in rats. Aripiprazole and a metabolite (2,3-DCPP) were clastogenic in the *in vitro* chromosomal aberration assay in CHL cells with and without metabolic activation. The metabolite, 2,3-DCPP, produced increases in numerical aberrations in the *in vitro* assay in CHL cells in the absence of metabolic activation. A positive response was obtained in the *in vivo* micronucleus assay in mice, however, the response was shown to be due to a mechanism not considered relevant to humans.

## Impairment of Fertility

Female rats were treated with oral doses of 2, 6, and 20 mg/kg/day (0.6, 2, and 6 times the maximum recommended human dose [MRHD] on a mg/m<sup>2</sup> basis) of aripiprazole from 2 weeks prior to mating through day 7 of gestation. Estrus cycle irregularities and increased corpora lutea were seen at all doses, but no impairment of fertility was seen. Increased pre-implantation loss was seen at 6 and 20 mg/kg, and decreased fetal weight was seen at 20 mg/kg.

Male rats were treated with oral doses of 20, 40, and 60 mg/kg/day (6, 13, and 19 times the MRHD on a mg/m<sup>2</sup> basis) of aripiprazole from 9 weeks prior to mating through mating. Disturbances in spermatogenesis were seen at 60 mg/kg, and prostate atrophy was seen at 40 and 60 mg/kg, but no impairment of fertility was seen.

## Pregnancy

### Pregnancy Category C

In animal studies, aripiprazole demonstrated developmental toxicity, including possible teratogenic effects in rats and rabbits.

Pregnant rats were treated with oral doses of 3, 10, and 30 mg/kg/day (1, 3, and 10 times the maximum recommended human dose [MRHD] on a mg/m<sup>2</sup> basis) of aripiprazole during the period of organogenesis. Gestation was slightly prolonged at 30 mg/kg. Treatment caused a slight delay in fetal development, as evidenced by decreased

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fetal weight (30 mg/kg), undescended testes (30 mg/kg), and delayed skeletal ossification (10 and 30 mg/kg). There were no adverse effects on embryofetal or pup survival. Delivered offspring had decreased bodyweights (10 and 30 mg/kg), and increased incidences of hepatodiaphragmatic nodules and diaphragmatic hernia at 30 mg/kg (the other dose groups were not examined for these findings). (A low incidence of diaphragmatic hernia was also seen in the fetuses exposed to 30 mg/kg.) Postnatally, delayed vaginal opening was seen at 10 and 30 mg/kg and impaired reproductive performance (decreased fertility rate, corpora lutea, implants, and live fetuses, and increased post-implantation loss, likely mediated through effects on female offspring) was seen at 30 mg/kg. Some maternal toxicity was seen at 30 mg/kg, however, there was no evidence to suggest that these developmental effects were secondary to maternal toxicity.

Pregnant rabbits were treated with oral doses of 10, 30, and 100 mg/kg/day (2, 3, and 11 times human exposure at MRHD based on AUC and 6, 19, and 65 times the MRHD based on  $\text{mg}/\text{m}^2$ ) of aripiprazole during the period of organogenesis. Decreased maternal food consumption and increased abortions were seen at 100 mg/kg. Treatment caused increased fetal mortality (100 mg/kg), decreased fetal weight (30 and 100 mg/kg), increased incidence of a skeletal abnormality (fused sternbrae at 30 and 100 mg/kg) and minor skeletal variations (100 mg/kg).

In a study in which rats were treated with oral doses of 3, 10, and 30 mg/kg/day (1, 3, and 10 times the MRHD on a  $\text{mg}/\text{m}^2$  basis) of aripiprazole perinatally and postnatally (from day 17 of gestation through day 21 postpartum), slight maternal toxicity and slightly prolonged gestation were seen at 30 mg/kg. An increase in stillbirths, and decreases in pup weight (persisting into adulthood) and survival, were seen at this dose.

There are no adequate and well-controlled studies in pregnant women. It is not known whether aripiprazole can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Aripiprazole should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

## Labor and Delivery

The effect of aripiprazole on labor and delivery in humans is unknown.

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## Nursing Mothers

Aripiprazole was excreted in milk of rats during lactation. It is not known whether aripiprazole or its metabolites are excreted in human milk. It is recommended that women receiving aripiprazole should not breast-feed.

## Pediatric Use

Safety and effectiveness in pediatric and adolescent patients have not been established.

## Geriatric Use

Of the 5592 patients treated with aripiprazole in premarketing clinical trials, 659 (12%) were  $\geq 65$  years old and 525 (9%) were  $\geq 75$  years old. The majority (91%) of the 659 patients were diagnosed with dementia of the Alzheimer's type.

Placebo-controlled studies of aripiprazole in schizophrenia did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. There was no effect of age on the pharmacokinetics of a single 15-mg dose of aripiprazole. Aripiprazole clearance was decreased by 20% in elderly subjects ( $\geq 65$  years) compared to younger adult subjects (18 to 64 years), but there was no detectable effect of age in the population pharmacokinetic analysis in schizophrenia patients.

Studies of elderly patients with psychosis associated with Alzheimer's disease have suggested that there may be a different tolerability profile in this population compared to younger patients with schizophrenia (see **PRECAUTIONS: Use in Patients with Concomitant Illness**). The safety and efficacy of ABILIFY in the treatment of patients with psychosis associated with Alzheimer's disease has not been established. If the prescriber elects to treat such patients with ABILIFY, vigilance should be exercised.

## ADVERSE REACTIONS

Aripiprazole has been evaluated for safety in 5592 patients who participated in multiple-dose, premarketing trials in schizophrenia, bipolar mania, and dementia of the Alzheimer's type, and who had approximately 3639 patient-years of exposure. A total of 1887 aripiprazole-treated patients were treated for at least 180 days and 1251 aripiprazole-treated patients had at least 1 year of exposure.

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The conditions and duration of treatment with aripiprazole included (in overlapping categories) double-blind, comparative and noncomparative open-label studies, inpatient and outpatient studies, fixed- and flexible-dose studies, and short- and longer-term exposure.

Adverse events during exposure were obtained by collecting volunteered adverse events, as well as results of physical examinations, vital signs, weights, laboratory analyses, and ECG. Adverse experiences were recorded by clinical investigators using terminology of their own choosing. In the tables and tabulations that follow, modified COSTART dictionary terminology has been used initially to classify reported adverse events into a smaller number of standardized event categories, in order to provide a meaningful estimate of the proportion of individuals experiencing adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. There was no attempt to use investigator causality assessments; ie, all reported events are included.

The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatment, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the adverse event incidence in the population studied.

### **Adverse Findings Observed in Short-Term, Placebo-Controlled Trials of Patients with Schizophrenia**

The following findings are based on a pool of five placebo-controlled trials (four 4-week and one 6-week) in which aripiprazole was administered in doses ranging from 2 to 30 mg/day.

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**Adverse Events Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials**

Overall, there was no difference in the incidence of discontinuation due to adverse events between aripiprazole-treated (7%) and placebo-treated (9%) patients. The types of adverse events that led to discontinuation were similar between the aripiprazole and placebo-treated patients.

**Adverse Events Occurring at an Incidence of 2% or More Among Aripiprazole-Treated Patients and Greater than Placebo in Short-Term, Placebo-Controlled Trials**

Table 1 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during acute therapy (up to 6 weeks), including only those events that occurred in 2% or more of patients treated with aripiprazole (doses  $\geq 2$  mg/day) and for which the incidence in patients treated with aripiprazole was greater than the incidence in patients treated with placebo.

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**Table 1: Treatment-Emergent Adverse Events in Short-Term, Placebo-Controlled Trials**

Body System Adverse Event	Percentage of Patients Reporting Event <sup>a</sup>	
	Aripiprazole (n=926)	Placebo (n=413)
<b>Body as a Whole</b>		
Headache	32	25
Asthenia	7	5
Fever	2	1
<b>Digestive System</b>		
Nausea	14	10
Vomiting	12	7
Constipation	10	8
<b>Nervous System</b>		
Anxiety	25	24
Insomnia	24	19
Lightheadedness	11	7
Somnolence	11	8
Akathisia	10	7
Tremor	3	2
<b>Respiratory System</b>		
Rhinitis	4	3
Coughing	3	2
<b>Skin and Appendages</b>		
Rash	6	5
<b>Special Senses</b>		
Blurred vision	3	1

<sup>a</sup> Events reported by at least 2% of patients treated with aripiprazole, except the following events, which had an incidence equal to or less than placebo: abdominal pain, accidental injury, back pain, dental pain, dyspepsia, diarrhea, dry mouth, myalgia, agitation, psychosis, extrapyramidal syndrome, hypertonia, pharyngitis, upper respiratory tract infection, dysmenorrhea, vaginitis.

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An examination of population subgroups did not reveal any clear evidence of differential adverse event incidence on the basis of age, gender, or race.

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## Dose-Related Adverse Events

Dose response relationships for the incidence of treatment-emergent adverse events were evaluated from four trials comparing various fixed doses (2, 10, 15, 20, and 30 mg/day) of aripiprazole to placebo. This analysis, stratified by study, indicated that the only adverse event to have a possible dose response relationship, and then most prominent only with 30 mg, was somnolence (placebo, 7.7%; 15 mg, 8.7%; 20 mg, 7.5%; 30 mg, 15.3%).

## Extrapyramidal Symptoms

In the short-term, placebo-controlled trials, the incidence of reported EPS for aripiprazole-treated patients was 6% vs. 6% for placebo. Objectively collected data from those trials on the Simpson Angus Rating Scale (for EPS), the Barnes Akathisia Scale (for akathisia), and the Assessments of Involuntary Movement Scales (for dyskinesias) also did not show a difference between aripiprazole and placebo, with the exception of the Barnes Akathisia Scale (aripiprazole, 0.08; placebo, -0.05).

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Similarly, in a long-term (26-week) placebo-controlled trial, objectively collected data on the Simpson Angus Rating Scale (for EPS), the Barnes Akathisia Scale (for akathisia), and the Assessments of Involuntary Movement Scales (for dyskinesias) did not show a difference between aripiprazole and placebo.

## Laboratory Test Abnormalities

A between group comparison for 4- to 6-week placebo-controlled trials revealed no medically important differences between the aripiprazole and placebo groups in the proportions of patients experiencing potentially clinically significant changes in routine serum chemistry, hematology, or urinalysis parameters. Similarly, there were no aripiprazole/placebo differences in the incidence of discontinuations for changes in serum chemistry, hematology, or urinalysis.

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In a long-term (26-week) placebo-controlled trial there were no medically important differences between the aripiprazole and placebo patients in the mean change from baseline in prolactin, fasting glucose, triglyceride, HDL, LDL, and total cholesterol measurements.

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## Weight Gain

In short-term trials, there was a slight difference in mean weight gain between aripiprazole and placebo patients (+0.7 kg vs. -0.05 kg, respectively), and also a difference in the proportion of patients meeting a weight gain criterion of  $\geq 7\%$  of body weight [aripiprazole (8%) compared to placebo (3%)].

Table 2 provides the weight change results from a long-term (26-week) placebo-controlled study of aripiprazole, both mean change from baseline and proportions of patients meeting a weight gain criterion of  $\geq 7\%$  of body weight relative to baseline, categorized by BMI at baseline:

**Table 2: Weight Change Results Categorized by BMI at Baseline: Placebo-Controlled Study in Schizophrenia, Safety Sample**

	BMI <23		BMI 23-27		BMI >27	
	Placebo	Aripiprazole	Placebo	Aripiprazole	Placebo	Aripiprazole
Mean change from baseline (kg)	-0.5	-0.5	-0.6	-1.3	-1.5	-2.1
% with $\geq 7\%$ increase BW	3.7%	6.8%	4.2%	5.1%	4.1%	5.7%

Table 3 provides the weight change results from a long-term (52-week) study of aripiprazole, both mean change from baseline and proportions of patients meeting a weight gain criterion of  $\geq 7\%$  of body weight relative to baseline, categorized by BMI at baseline:

**Table 3: Weight Change Results Categorized by BMI at Baseline**

	BMI <23	BMI 23-27	BMI >27
Mean change from baseline (kg)	2.6	1.4	-1.2
% with $\geq 7\%$ increase BW	30%	19%	8%

## ECG Changes

Between group comparisons for pooled, placebo-controlled trials revealed no significant differences between aripiprazole and placebo in the proportion of patients experiencing potentially important changes in ECG parameters; in fact, within the dose range of 10 to

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30 mg/day, aripiprazole tended to slightly shorten the QTc interval. Aripiprazole was associated with a median increase in heart rate of 4 beats per minute compared to a 1 beat per minute increase among placebo patients.

## **Additional Findings Observed in Clinical Trials**

### **Adverse Events in a Long-Term, Double-Blind, Placebo-Controlled Trial**

The adverse events reported in a 26-week, double-blind trial comparing ABILIFY and placebo were generally consistent with those reported in the short-term, placebo-controlled trials, except for a higher incidence of tremor [9% (13/153) for ABILIFY vs. 1% (2/153) for placebo]. In this study, the majority of the cases of tremor were of mild intensity (9/13 mild and 4/13 moderate), occurred early in therapy (9/13 ≤49 days) and were of limited duration (9/13 ≤10 days). Tremor infrequently led to discontinuation (<1%) of ABILIFY. In addition, in a long-term (52-week) active controlled study, the incidence of tremor for ABILIFY was 4% (34/859).

### **Other Adverse Events Observed During the Premarketing Evaluation of Aripiprazole**

Following is a list of modified COSTART terms that reflect treatment-emergent adverse events as defined in the introduction to the **ADVERSE REACTIONS** section reported by patients treated with aripiprazole at multiple doses  $\geq 2$  mg/day during any phase of a trial within the database of 5592 patients. All reported events are included except those already listed in Table 1, or other parts of the **ADVERSE REACTIONS** section, those considered in the **WARNINGS** or **PRECAUTIONS**, those event terms which were so general as to be uninformative, events reported with an incidence of  $<0.05\%$  and which did not have a substantial probability of being acutely life-threatening, events that are otherwise common as background events, and events considered unlikely to be drug related. It is important to emphasize that, although the events reported occurred during treatment with aripiprazole, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

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*Body as a Whole: Frequent* - flu syndrome, peripheral edema, chest pain, neck pain, neck rigidity; *Infrequent* - pelvic pain, suicide attempt, face edema, malaise, photosensitivity, arm rigidity, jaw pain, chills, bloating, jaw tightness, enlarged abdomen, chest tightness; *Rare* - throat pain, back tightness, head heaviness, moniliasis, throat tightness, leg rigidity, neck tightness, Mendelson's syndrome, heat stroke.

*Cardiovascular System: Frequent* - hypertension, tachycardia, hypotension, bradycardia; *Infrequent* - palpitation, hemorrhage, myocardial infarction, prolonged QT interval, cardiac arrest, atrial fibrillation, heart failure, AV block, myocardial ischemia, phlebitis, deep vein thrombosis, angina pectoris, extrasystoles; *Rare* - vasovagal reaction, cardiomegaly, atrial flutter, thrombophlebitis.

*Digestive System: Frequent* - anorexia, nausea and vomiting; *Infrequent* - increased appetite, gastroenteritis, dysphagia, flatulence, gastritis, tooth caries, gingivitis, hemorrhoids, gastroesophageal reflux, gastrointestinal hemorrhage, periodontal abscess, tongue edema, fecal incontinence, colitis, rectal hemorrhage, stomatitis, mouth ulcer, cholecystitis, fecal impaction, oral moniliasis, cholelithiasis, eructation, intestinal obstruction, peptic ulcer; *Rare* - esophagitis, gum hemorrhage, glossitis, hematemesis, melena, duodenal ulcer, cheilitis, hepatitis, hepatomegaly, pancreatitis, intestinal perforation.

*Endocrine System: Infrequent* - hypothyroidism; *Rare* - goiter, hyperthyroidism.

*Hemic/Lymphatic System: Frequent* - ecchymosis, anemia; *Infrequent* - hypochromic anemia, leukopenia, leukocytosis, lymphadenopathy, thrombocytopenia; *Rare* - eosinophilia, thrombocythemia, macrocytic anemia.

*Metabolic and Nutritional Disorders: Frequent* - weight loss, creatine phosphokinase increased; *Infrequent* - dehydration, edema, hypercholesteremia, hyperglycemia, hypokalemia, diabetes mellitus, SGPT increased, hyperlipemia, hypoglycemia, thirst, BUN increased, hyponatremia, SGOT increased, alkaline phosphatase increased, iron deficiency anemia, creatinine increased, bilirubinemia, lactic dehydrogenase increased, obesity; *Rare* - hyperkalemia, gout, hypernatremia, cyanosis, hyperuricemia, hypoglycemic reaction.

*Musculoskeletal System: Frequent* - muscle cramp; *Infrequent* - arthralgia, bone pain, myasthenia, arthritis, arthrosis, muscle weakness, spasm, bursitis; *Rare* - rhabdomyolysis, tendonitis, tenosynovitis, rheumatoid arthritis, myopathy.

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*Nervous System: Frequent* - depression, nervousness, increased salivation, hostility, suicidal thought, manic reaction, abnormal gait, confusion, cogwheel rigidity; *Infrequent* - dystonia, twitch, impaired concentration, paresthesia, vasodilation, hypesthesia, extremity tremor, impotence, bradykinesia, decreased libido, panic attack, apathy, dyskinesia, hypersomnia, vertigo, dysarthria, tardive dyskinesia, ataxia, impaired memory, stupor, increased libido, amnesia, cerebrovascular accident, hyperactivity, depersonalization, hypokinesia, restless leg, myoclonus, dysphoria, neuropathy, increased reflexes, slowed thinking, hyperkinesia, hyperesthesia, hypotonia, oculogyric crisis; *Rare* - delirium, euphoria, buccoglossal syndrome, akinesia, blunted affect, decreased consciousness, incoordination, cerebral ischemia, decreased reflexes, obsessive thought, intracranial hemorrhage.

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*Respiratory System: Frequent* - dyspnea, pneumonia; *Infrequent* - asthma, epistaxis, hiccup, laryngitis; *Rare* - hemoptysis, aspiration pneumonia, increased sputum, dry nasal passages, pulmonary edema, pulmonary embolism, hypoxia, respiratory failure, apnea.

*Skin and Appendages: Frequent* - dry skin, pruritus, sweating, skin ulcer; *Infrequent* - acne, vesiculobullous rash, eczema, alopecia, psoriasis, seborrhea; *Rare* - maculopapular rash, exfoliative dermatitis, urticaria.

*Special Senses: Frequent* - conjunctivitis, ear pain; *Infrequent* - dry eye, eye pain, tinnitus, otitis media, cataract, altered taste, blepharitis; *Rare* - increased lacrimation, frequent blinking, otitis externa, amblyopia, deafness, diplopia, eye hemorrhage, photophobia.

*Urogenital System: Frequent* - urinary incontinence; *Infrequent* - cystitis, urinary frequency, leukorrhea, urinary retention, hematuria, dysuria, amenorrhea, abnormal ejaculation, vaginal hemorrhage, vaginal moniliasis, kidney failure, uterus hemorrhage, menorrhagia, albuminuria, kidney calculus, nocturia, polyuria, urinary urgency; *Rare* - breast pain, cervicitis, female lactation, anorgasmy, urinary burning, glycosuria, gynecomastia, urolithiasis, priapism.

## DRUG ABUSE AND DEPENDENCE

### Controlled Substance

ABILIFY (aripiprazole) is not a controlled substance.

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## Abuse and Dependence

Aripiprazole has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. In physical dependence studies in monkeys, withdrawal symptoms were observed upon abrupt cessation of dosing. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of ABILIFY misuse or abuse (eg, development of tolerance, increases in dose, drug-seeking behavior).

## OVERDOSAGE

### Human Experience

In premarketing clinical studies, involving more than 5500 patients, accidental or intentional acute overdosage of aripiprazole was identified in seven patients. In the two patients taking the largest identified amount, 180 mg, the only symptoms reported were somnolence and vomiting in one of the two patients. In the patients who were evaluated in hospital settings, including the two patients taking 180 mg, there were no observations indicating an adverse change in vital signs, laboratory assessments, or ECG. An uneventful, accidental overdose (15 mg) occurred in a non-patient, an 18-month-old child, with concomitant ingestion of ATIVAN<sup>®</sup> (2 mg).

### Management of Overdosage

No specific information is available on the treatment of overdose with aripiprazole. An electrocardiogram should be obtained in case of overdosage and, if QTc interval prolongation is present, cardiac monitoring should be instituted. Otherwise, management of overdose should concentrate on supportive therapy, maintaining an adequate airway, oxygenation and ventilation, and management of symptoms. Close medical supervision and monitoring should continue until the patient recovers.

*Charcoal:* In the event of an overdose of ABILIFY, an early charcoal administration may be useful in partially preventing the absorption of aripiprazole.

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ATIVAN<sup>®</sup> is a registered trademark of Wyeth Laboratories, a Wyeth-Ayerst Company.

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Administration of 50 g of activated charcoal, one hour after a single 15-mg oral dose of aripiprazole, decreased the mean AUC and Cmax of aripiprazole by 50%.

*Hemodialysis:* Although there is no information on the effect of hemodialysis in treating an overdose with aripiprazole, hemodialysis is unlikely to be useful in overdose management since aripiprazole is highly bound to plasma proteins.

## DOSAGE AND ADMINISTRATION

### Usual Dose

The recommended starting and target dose for ABILIFY is 10 or 15 mg/day administered on a once-a-day schedule without regard to meals. ABILIFY has been systematically evaluated and shown to be effective in a dose range of 10 to 30 mg/day, however, doses higher than 10 or 15 mg/day, the lowest doses in these trials, were not more effective than 10 or 15 mg/day. Dosage increases should not be made before 2 weeks, the time needed to achieve steady state.

### Dosage in Special Populations

Dosage adjustments are not routinely indicated on the basis of age, gender, race, or renal or hepatic impairment status (see CLINICAL PHARMACOLOGY: Special Populations).

*Dosage adjustment for patients taking aripiprazole concomitantly with potential CYP3A4 inhibitors:* When concomitant administration of ketoconazole with aripiprazole occurs, aripiprazole dose should be reduced to one-half of the usual dose. When the CYP3A4 inhibitor is withdrawn from the combination therapy, aripiprazole dose should then be increased.

*Dosage adjustment for patients taking aripiprazole concomitantly with potential CYP2D6 inhibitors:* When concomitant administration of potential CYP2D6 inhibitors such as quinidine, fluoxetine, or paroxetine with aripiprazole occurs, aripiprazole dose should be reduced at least to one-half of its normal dose. When the CYP2D6 inhibitor is withdrawn from the combination therapy, aripiprazole dose should then be increased.

*Dosage adjustment for patients taking potential CYP3A4 inducers:* When a potential CYP3A4 inducer such as carbamazepine is added to aripiprazole therapy, the

aripiprazole dose should be doubled (to 20 or 30 mg). Additional dose increases should be based on clinical evaluation. When carbamazepine is withdrawn from the combination therapy, the aripiprazole dose should be reduced to 10 to 15 mg.

### Maintenance Therapy

While there is no body of evidence available to answer the question of how long a patient treated with aripiprazole should remain on it, systematic evaluation of patients with schizophrenia who had been symptomatically stable on other antipsychotic medications for periods of 3 months or longer, were discontinued from those medications, and were then administered ABILIFY 15 mg/day and observed for relapse during a period of up to 26 weeks demonstrated a benefit of such maintenance treatment (see CLINICAL PHARMACOLOGY: Clinical Studies). Patients should be periodically reassessed to determine the need for maintenance treatment.

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### Switching from Other Antipsychotics

There are no systematically collected data to specifically address switching patients with schizophrenia from other antipsychotics to ABILIFY or concerning concomitant administration with other antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some patients with schizophrenia, more gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized.

### ANIMAL TOXICOLOGY

Aripiprazole produced retinal degeneration in albino rats in a 26-week chronic toxicity study at a dose of 60 mg/kg and in a 2-year carcinogenicity study at doses of 40 and 60 mg/kg. The 40- and 60-mg/kg doses are 13 and 19 times the maximum recommended human dose (MRHD) based on mg/m<sup>2</sup> and 7 to 14 times human exposure at MRHD based on AUC. Evaluation of the retinas of albino mice and of monkeys did not reveal evidence of retinal degeneration. Additional studies to further evaluate the mechanism have not been performed. The relevance of this finding to human risk is unknown.

### HOW SUPPLIED

ABILIFY™ (aripiprazole) Tablets are available in the following strengths and packages.

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The 5-mg ABILIFY tablets are blue, modified rectangular tablets, debossed on one side with "A-007" and "5".

Bottles of 30 NDC 59148-007-13

Blister of 100 NDC 59148-007-35

The 10-mg ABILIFY tablets are pink, modified rectangular tablets, debossed on one side with "A-008" and "10".

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Bottles of 30 NDC 59148-008-13

Blister of 100 NDC 59148-008-35

The 15-mg ABILIFY tablets are yellow, round tablets, debossed on one side with "A-009" and "15".

Bottles of 30 NDC 59148-009-13

Blister of 100 NDC 59148-009-35

The 20-mg ABILIFY tablets are white, round tablets, debossed on one side with "A-010" and "20".

Bottles of 30 NDC 59148-010-13

Blister of 100 NDC 59148-010-35

The 30-mg ABILIFY tablets are pink, round tablets, debossed on one side with "A-011" and "30".

Bottles of 30 NDC 59148-011-13

Blister of 100 NDC 59148-011-35

## Storage

Store at 25° C (77° F); excursions permitted to 15-30° C (59-86° F) [see USP Controlled Room Temperature].

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Bristol-Myers Squibb Company, Princeton, NJ 08543 USA

Manufactured and Distributed by Bristol-Myers Squibb Company, Princeton, NJ 08543  
USA

U.S. Patent Nos. 4,734,416 and 5,006,528

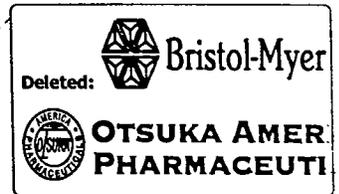
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