

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21-436/S-007 & 21-713/S-004

Trade Name: Abilify Tablets & Oral Solution

Generic Name: aripiprazole

Sponsor: Otsuka Pharmaceutical Company

Approval Date: 06/21/2005

Indications: For the treatment of schizophrenia and acute manic and mixed episodes associated with Bipolar Disorder.

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APPLICATION NUMBER:
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APPLICATION NUMBER:
21-436/S-007 & 21-713/S-004

APPROVAL LETTER



NDA 21-436 / S-007

NDA 21-713 / S-004

Bristol-Myers Squibb Pharmaceutical Research Institute
Attention: Susan H. Behling
5 Research Parkway
P.O. Box 5100
Wallingford, CT 06492-7660

Dear Ms. Behling:

Please refer to your supplemental new drug application (sNDA) dated May 14, 2004, received May 18, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Abilify (aripiprazole) Tablets. Refer also to your sNDA dated February 15, 2005, received February 16, 2005 for Abilify (aripiprazole) Oral Solution.

We acknowledge receipt of your submission of February 15, 2005, which constituted a complete response to our action letter of November 2, 2004.

These "Changes Being Effected" supplemental new drug applications provide for revisions to the OVERDOSAGE/Human Experience section of Abilify labeling as follows:

OVERDOSAGE

MedDRA terminology has been used to classify the adverse events.

Human Experience

A total of 76 cases of deliberate or accidental overdose with aripiprazole have been reported worldwide. These include overdoses with aripiprazole alone and in combination with other substances. No fatality was reported from these cases. Of the 44 cases with known outcome, 33 recovered without sequelae and one recovered with sequelae (mydriasis and feeling abnormal). The largest known acute ingestion with a known outcome involved 1080 mg of aripiprazole (36 times the maximum recommended daily dose) in a patient who fully recovered. Included in the 76 cases are 10 cases of deliberate or accidental overdose in children (age 12 and younger) involving aripiprazole ingestions up to 195 mg with no fatalities.

Common adverse events (reported in at least 5% of all overdose cases) reported with aripiprazole overdose (alone or in combination with other substances) include vomiting, somnolence, and tremor. Other clinically important signs and symptoms observed in one or more patients with aripiprazole overdoses (alone or with other substances) include acidosis, aggression, aspartate aminotransferase increased, atrial fibrillation, bradycardia, coma, confusional state, convulsion, blood creatine phosphokinase increased, depressed level of consciousness, hypertension, hypokalemia, hypotension, lethargy, loss of consciousness, QRS complex prolonged, QT prolonged, pneumonia aspiration, respiratory arrest, status epilepticus and tachycardia.

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We have completed our review of these supplemental new drug applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the final printed labeling (FPL) submitted on February 15, 2005 (attached).

We remind you that you must comply with the requirements for an approved NDA set forth under 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

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/s/

Russell Katz
6/21/05 03:20:49 PM

**CENTER FOR DRUG EVALUATION AND
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APPLICATION NUMBER:
21-436/S-007 & 21-713/S-004

APPROVABLE LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-436 / S-007

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

Dear Dr. Mallikaarjun:

Please refer to your supplemental new drug application dated May 14, 2004, received May 18, 2004, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Abilify (aripiprazole) Tablets.

This "Changes Being Effected" supplemental new drug application provides for revised labeling updating the OVERDOSAGE / Human Experience subsection and incorporating a postmarketing section under ADVERSE REACTIONS.

We completed our review of this application, and it is approvable. Before the application may be approved, however, you must address the following:

1. The revised OVERDOSAGE / Human Experience subsection cannot be completely evaluated based on the information provided. It appears that you intend to provide a cumulative update of human overdose experience but, in support of this update, have provided data from only a six-month period. Data from cumulative overdose experience are required to support the revision of this information.

To describe the cumulative overdose experience in a more complete and systematic fashion, we request that you revise the language for this subsection based on the review of the cumulative safety database using a recent cut-off date for safety data and the following format:

OVERDOSAGE

Human Experience

A total of ___ cases of deliberate or accidental overdose with aripiprazole have been reported worldwide [] These include overdoses with aripiprazole alone and in combination with other substances. []

--	--

ingestion with a known outcome involved ___ mg of aripiprazole (___ times the maximum recommended daily dose) in a patient who ___ [died, recovered fully, or recovered with sequelae]. Included in the above are ___ cases of deliberate or

b(4)

accidental overdosage in children (age 12 and younger) involving

b(4)

Common adverse events with aripiprazole overdosage (alone or in combination with other substances) include _____ [list all events by COSTART term reported in at least 5% of all overdose cases]. Other clinically important signs and symptoms observed

b(4)

In support of the revised language, please submit a line listing of all overdose cases for our review. This listing should include the following information:

- Patient identification (e.g., case number).
 - Age (years).
 - Amount of aripiprazole ingested (mg).
 - Other substances ingested.
 - Associated adverse events (by COSTART or MedDRA term).
 - Outcome (fatal, fully recovered, recovered with sequelae (specify), or unknown).
2. The new postmarketing reports subsection has already been reviewed and approved on September 29, 2004 as part of the NDA 21-436/ S-002 application (aripiprazole for the treatment of acute bipolar mania).

To facilitate review of your submission, provide a highlighted or marked-up copy that shows the changes. All previous revisions, as reflected in the most recently approved package insert, must be included.

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

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/s/

Russell Katz
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21-436/S-007 & 21-713/S-004

LABELING

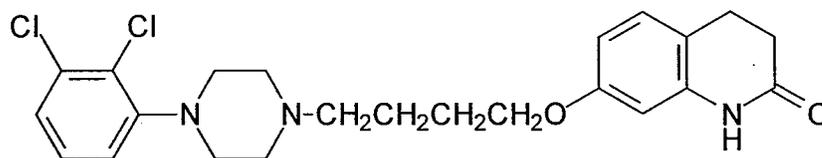
Rx only

ABILIFY® (aripiprazole) Tablets

ABILIFY® (aripiprazole) Oral Solution

DESCRIPTION

ABILIFY® (aripiprazole) is a psychotropic drug that is available as tablets and in solution for oral administration. Aripiprazole is 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydrocarbostyril. 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 cornstarch, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate and microcrystalline cellulose. Colorants include ferric oxide (yellow or red) and FD&C Blue No. 2 Aluminum Lake.

ABILIFY is also available as a 1 mg/mL oral solution. The inactive ingredients for this solution include fructose, glycerin, dl-lactic acid, methylparaben, propylene glycol, propylparaben, sodium hydroxide, sucrose, and purified water. The oral solution is flavored with natural orange cream and other natural flavors.

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 D₄, serotonin 5-HT_{2C} and 5-HT₇, alpha₁-adrenergic and histamine H₁ 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 (IC₅₀>1000 nM). Aripiprazole functions as a partial agonist at the dopamine D₂ 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 and bipolar disorder, is unknown. However, it has been proposed that the efficacy of aripiprazole is mediated through a combination of partial agonist activity at D₂ and 5-HT_{1A} receptors and antagonist activity at 5-HT_{2A} receptors. Actions at receptors other than D₂, 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 alpha₁ 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 D₂ 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

Tablet

Aripiprazole is well absorbed after administration of the tablet, 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.

Oral Solution

Aripiprazole is well absorbed when administered orally as the solution. At equivalent doses, the plasma concentrations of aripiprazole from the solution were higher than that from the tablet formulation. In a relative bioavailability study comparing the pharmacokinetics of 30 mg aripiprazole as the oral solution to 30 mg aripiprazole tablets in healthy subjects, the solution to tablet ratios of geometric mean C_{max} and AUC values were 122% and 114%, respectively (see **DOSAGE AND ADMINISTRATION**.) The single-dose pharmacokinetics of aripiprazole were linear and dose-proportional between the doses of 5 to 30 mg.

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 D₂ 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 [¹⁴C]-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_{max} 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_{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 H₂ 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_{max} 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_{max} 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_{max} 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

Schizophrenia

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 ≥ 5 (minimally worse), scores ≥ 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.

Bipolar Mania

The efficacy of ABILIFY in the treatment of acute manic episodes was established in two 3-week, placebo-controlled trials in hospitalized patients who met the DSM-IV criteria for Bipolar I Disorder with manic or mixed episodes (in one trial, 21% of placebo and 42% of ABILIFY-treated patients had data beyond two weeks). These trials included patients with or without psychotic features and with or without a rapid-cycling course.

The primary instrument used for assessing manic symptoms was the Young Mania Rating Scale (Y-MRS), an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology (irritability, disruptive/aggressive behavior, sleep, elevated mood, speech, increased activity, sexual interest, language/thought disorder, thought content, appearance, and insight) in a range from 0 (no manic features) to 60 (maximum score). A key secondary instrument included the Clinical Global Impression - Bipolar (CGI-BP) scale.

In the two positive, 3-week, placebo-controlled trials (n=268; n=248) which evaluated ABILIFY 15 or 30 mg/day, once daily (with a starting dose of 30 mg/day), ABILIFY was superior to placebo in the reduction of Y-MRS total score and CGI-BP Severity of Illness score (mania).

An examination of population subgroups did not reveal any clear evidence of differential responsiveness on the basis of age and gender; however, there were insufficient numbers of patients in each of the ethnic groups to adequately assess inter-group differences.

INDICATIONS AND USAGE

Schizophrenia

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**).

Bipolar Mania

ABILIFY is indicated for the treatment of acute manic and mixed episodes associated with Bipolar Disorder.

The efficacy of ABILIFY was established in two placebo-controlled trials (3 week) of inpatients with DSM-IV criteria for Bipolar I Disorder who were experiencing an acute manic or mixed episode with or without psychotic features (see **CLINICAL PHARMACOLOGY**). However, the effectiveness of ABILIFY for longer-term use, that is, for more than 3 weeks of treatment of an acute episode, and for prophylactic use in mania, has not been established in controlled clinical trials. Therefore, physicians who elect to use ABILIFY for extended periods should periodically re-evaluate the long-term risks and benefits 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.

Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients with Dementia

In placebo-controlled clinical studies (two flexible dose and one fixed dose study) of dementia-related psychosis, there was an increased incidence of cerebrovascular adverse events (eg, stroke, transient ischemic attack), including fatalities, in aripiprazole-treated patients (mean age: 84 years; range: 78-88 years). In the fixed-dose study, there was a statistically significant dose response relationship for cerebrovascular adverse events in patients treated with aripiprazole. Aripiprazole is not approved for the treatment of

patients with dementia-related psychosis. (See also **PRECAUTIONS: Use in Patients with Concomitant Illness: Safety Experience in Elderly Patients with Psychosis Associated with Alzheimer's Disease.**)

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. There have been few reports of hyperglycemia in patients treated with ABILIFY. Although fewer patients have been treated with ABILIFY, it is not known if this more limited experience is the sole reason for the paucity of such reports. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies which did not include ABILIFY suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics included in these studies. Because ABILIFY was not marketed at the time these studies were performed, it is not known if ABILIFY is associated with this increased risk. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (eg, obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

PRECAUTIONS

General

Orthostatic Hypotension

Aripiprazole may be associated with orthostatic hypotension, perhaps due to its α_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 orthostatic hypotension-associated events from short-term, placebo-controlled trials in bipolar mania (n=597) on ABILIFY included: orthostatic hypotension (placebo 0%, aripiprazole 0.7%), orthostatic lightheadedness (placebo 0.5%, aripiprazole 0.5%), and syncope (placebo 0.9%, aripiprazole 0.5%).

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 (in schizophrenia: 14% among aripiprazole-treated patients and 12% among placebo-treated patients and in bipolar mania: 3% among aripiprazole-treated patients and 2% 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 with schizophrenia in short-term, placebo-controlled trials. In short-term, placebo-controlled clinical trials of patients with bipolar mania, 0.3% (2/597) of aripiprazole-treated patients and 0.2% (1/436) of placebo-treated patients experienced seizures. 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 of schizophrenia, 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 with schizophrenia on ABILIFY in short-term, placebo-controlled trials. In short-term, placebo-controlled trials of bipolar mania, somnolence was reported in 14% of patients on ABILIFY compared to 7% of patients on placebo, but did not lead to discontinuation of any patients with bipolar mania. 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 bipolar disorder, and close supervision of high-risk patients should accompany drug therapy. Prescriptions

for ABILIFY should be written for the smallest quantity 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. (See also **WARNINGS: Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients with Dementia.**)

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.

Sugar Content

Patients should be advised that each mL of ABILIFY oral solution contains 400 mg of sucrose and 200 mg of fructose.

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 α_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_{max} 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/m²,

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^2). 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^2). 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^2); 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^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 mg/kg/day (0.6, 2, and 6 times the maximum recommended human dose [MRHD] on a mg/m² 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/m² 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/m² 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 mg/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 mg/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 7951 patients treated with aripiprazole in premarketing clinical trials, 991 (12%) were ≥ 65 years old and 789 (10%) were ≥ 75 years old. The majority (88%) of the 991 patients were diagnosed with dementia of the Alzheimer's type.

Placebo-controlled studies of aripiprazole in schizophrenia or bipolar mania 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 (≥ 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 7951 patients who participated in multiple-dose, premarketing trials in schizophrenia, bipolar mania, and dementia of the Alzheimer's type, and who had approximately 5235 patient-years of exposure. A total of 2280 aripiprazole-treated patients were treated for at least 180 days and 1558 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 Findings Observed in Short-Term, Placebo-Controlled Trials of Patients with Bipolar Mania

The following findings are based on a pool of 3-week, placebo-controlled, bipolar mania trials in which aripiprazole was administered at doses of 15 or 30 mg/day.

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

Overall, in patients with bipolar mania, there was no difference in the incidence of discontinuation due to adverse events between aripiprazole-treated (11%) and placebo-treated (9%) patients. The types of adverse events that led to discontinuation were similar between the aripiprazole and placebo-treated patients.

Commonly Observed Adverse Events in Short-Term, Placebo-Controlled Trials of Patients with Bipolar Mania

Commonly observed adverse events associated with the use of aripiprazole in patients with bipolar mania (incidence of 5% or greater and aripiprazole incidence at least twice that for placebo) are shown in Table 1. There were no adverse events in the short-term trials of schizophrenia that met these criteria.

Table 1: Commonly Observed Adverse Events in Short-Term, Placebo-Controlled Trials of Patients with Bipolar Mania

Adverse Event	Percentage of Patients Reporting Event	
	Aripiprazole (n=597)	Placebo (n=436)
Accidental Injury	6	3
Constipation	13	6
Akathisia	15	4

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 2 enumerates the pooled incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during acute therapy (up to 6 weeks in schizophrenia and up to 3 weeks in bipolar mania), including only those events that occurred in 2% or more of patients treated with aripiprazole (doses ≥ 2 mg/day) and for which the incidence in patients treated with aripiprazole was greater than the incidence in patients treated with placebo in the combined dataset.

Table 2: Treatment-Emergent Adverse Events in Short-Term, Placebo-Controlled Trials

Body System Adverse Event	Percentage of Patients Reporting Event ^a	
	Aripiprazole (n=1523)	Placebo (n=849)
Body as a Whole		
Headache	31	26
Asthenia	8	7
Accidental Injury	5	4
Peripheral Edema	2	1
Cardiovascular System		
Hypertension	2	1
Digestive System		
Nausea	16	12
Dyspepsia	15	13
Vomiting	11	6
Constipation	11	7
Musculoskeletal System		
Myalgia	4	3
Nervous System		
Agitation	25	24
Anxiety	20	17
Insomnia	20	15
Somnolence	12	8
Akathisia	12	5
Lightheadedness	11	8
Extrapyramidal Syndrome	6	4
Tremor	4	3
Increased Salivation	3	1
Respiratory System		
Pharyngitis	4	3
Rhinitis	4	3
Coughing	3	2
Special Senses		
Blurred Vision	3	1

^a 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, back pain, dental pain, diarrhea, dry mouth, anorexia, psychosis, hypertonia, upper respiratory tract infection, rash, vaginitis, dysmenorrhea.

^f Percentage based on gender total.

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

Schizophrenia

Dose response relationships for the incidence of treatment-emergent adverse events were evaluated from four trials in patients with schizophrenia 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 of schizophrenia, the incidence of reported EPS for aripiprazole-treated patients was 6% vs. 6% for placebo. In the short-term, placebo-controlled trials in bipolar mania, the incidence of reported EPS-related events excluding events related to akathisia for aripiprazole-treated patients was 17% vs. 12% for placebo. In the short-term, placebo-controlled trials in bipolar mania, the incidence of akathisia-related events for aripiprazole-treated patients was 15% vs. 4% for placebo. Objectively collected data from those trials was collected on the Simpson Angus Rating Scale (for EPS), the Barnes Akathisia Scale (for akathisia) and the Assessments of Involuntary Movement Scales (for dyskinesias). In the schizophrenia trials, the objectively collected data did not show a difference between aripiprazole and placebo, with the exception of the Barnes Akathisia Scale (aripiprazole, 0.08; placebo, -0.05). In the bipolar mania trials, the Simpson Angus Rating Scale and the Barnes Akathisia Scale showed a significant difference between aripiprazole and placebo (aripiprazole, 0.61; placebo, 0.03 and aripiprazole, 0.25; placebo, -0.06). Changes in the Assessments of Involuntary Movement Scales were similar for the aripiprazole and placebo groups.

Similarly, in a long-term (26-week), placebo-controlled trial of schizophrenia, 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 3- 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 4- to 6- week trials in schizophrenia, 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%)]. In 3-week trials in mania, the mean weight gain for aripiprazole and placebo patients was 0.0 kg vs. -0.2 kg, respectively. The proportion of patients meeting a weight gain criterion of $\geq 7\%$ of body weight was aripiprazole (3%) compared to placebo (2%).

Table 3 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 3: 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 4 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 4: Weight Change Results Categorized by BMI at Baseline: Active-Controlled Study in Schizophrenia, Safety Sample

	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 in patients with schizophrenia, 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 ≤ 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 ≥ 2 mg/day during any phase of a trial within the database of 7951 patients. All reported events are included except those already listed in Table 2, 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 $\leq 0.05\%$ 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, fever, chest pain, rigidity (including neck and extremity), neck pain, pelvic pain; *Infrequent* - face edema, suicide attempt, malaise, migraine, chills, photosensitivity, tightness (including abdomen, back, extremity, head, jaw, neck, and tongue), jaw pain, bloating, enlarged abdomen, chest tightness, throat pain; *Rare* - moniliasis, head heaviness, throat tightness, Mendelson's syndrome, heat stroke.

Cardiovascular System: Frequent - tachycardia (including ventricular and supraventricular), hypotension, bradycardia; *Infrequent* - palpitation, hemorrhage, heart failure, myocardial infarction, cardiac arrest, atrial fibrillation, AV block, prolonged QT interval, extrasystoles, myocardial ischemia, deep vein thrombosis, angina pectoris, pallor, cardiopulmonary arrest, phlebitis; *Rare* - bundle branch block, atrial flutter, vasovagal reaction, cardiomegaly, thrombophlebitis, cardiopulmonary failure.

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

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

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

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

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

Nervous System: Frequent - depression, nervousness, schizophrenic reaction, hallucination, hostility, confusion, paranoid reaction, suicidal thought, abnormal gait, manic reaction, delusions, abnormal dream; *Infrequent* - emotional lability, twitch, cogwheel rigidity, impaired concentration, dystonia, vasodilation, paresthesia, impotence, extremity tremor, hypesthesia, vertigo, stupor, bradykinesia, apathy, panic attack, decreased libido, hypersomnia, dyskinesia, manic depressive reaction, ataxia, visual hallucination, cerebrovascular accident, hypokinesia, depersonalization, impaired memory, delirium, dysarthria, tardive dyskinesia, amnesia, hyperactivity, increased libido, myoclonus, restless leg, neuropathy, dysphoria, hyperkinesia, cerebral ischemia, increased reflexes, akinesia, decreased consciousness, hyperesthesia, slowed thinking;

Rare - blunted affect, euphoria, incoordination, oculogyric crisis, obsessive thought, hypotonia, buccoglossal syndrome, decreased reflexes, derealization, intracranial hemorrhage.

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

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

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

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

Other Events Observed During the Postmarketing Evaluation of Aripiprazole

Voluntary reports of adverse events in patients taking aripiprazole that have been received since market introduction and not listed above that may have no causal relationship with the drug include rare occurrences of allergic reaction (eg, anaphylactic reaction, angioedema, laryngospasm, pruritis, or urticaria).

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

MedDRA terminology has been used to classify the adverse events.

Human Experience

A total of 76 cases of deliberate or accidental overdose with aripiprazole have been reported worldwide. These include overdoses with aripiprazole alone and in combination with other substances. No fatality was reported from these cases. Of the 44 cases with known outcome, 33 recovered without sequelae and one recovered with sequelae (mydriasis and feeling abnormal). The largest known acute ingestion with a known outcome involved 1080 mg of aripiprazole (36 times the maximum recommended daily dose) in a patient who fully recovered. Included in the 76 cases are 10 cases of deliberate or accidental overdose in children (age 12 and younger) involving aripiprazole ingestions up to 195 mg with no fatalities.

Common adverse events (reported in at least 5% of all overdose cases) reported with aripiprazole overdose (alone or in combination with other substances) include vomiting, somnolence, and tremor. Other clinically important signs and symptoms observed in one or more patients with aripiprazole overdoses (alone or with other substances) include acidosis, aggression, aspartate aminotransferase increased, atrial fibrillation, bradycardia, coma, confusional state, convulsion, blood creatine phosphokinase increased, depressed level of consciousness, hypertension, hypokalaemia, hypotension, lethargy, loss of consciousness, QRS complex prolonged, QT prolonged, pneumonia aspiration, respiratory arrest, status epilepticus and tachycardia.

Management of Overdosage

No specific information is available on the treatment of overdose with aripiprazole. An electrocardiogram should be obtained in case of overdose 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. Administration of 50 g of activated charcoal, one hour after a single 15-mg oral dose of aripiprazole, decreased the mean AUC and C_{max} 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

Schizophrenia

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, when administered as the tablet formulation, 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.

Bipolar Mania

Usual Dose

In clinical trials, the starting dose was 30 mg given once a day. A dose of 30 mg/day was found to be effective when administered as the tablet formulation. Approximately 15% of patients had their dose decreased to 15 mg based on assessment of tolerability. The safety of doses above 30 mg/day has not been evaluated in clinical trials.

Dosage in Special Populations

See *Dosage in Special Populations* under **DOSAGE AND ADMINISTRATION: Schizophrenia**.

Maintenance Treatment

There is no body of evidence available from controlled trials to guide a clinician in the longer-term management of a patient who improves during treatment of an acute manic episode with aripiprazole. While it is generally agreed that pharmacological treatment beyond an acute response in mania is desirable, both for maintenance of the initial response and for prevention of new manic episodes, there are no systematically obtained data to support the use of aripiprazole in such longer-term treatment (ie, beyond 3 weeks).

Oral Solution

The oral solution can be given on a mg-per-mg basis in place of the 5-, 10-, 15-, or 20-mg tablet strengths. Solution doses can be substituted for the tablet doses on a mg-per-mg basis up to 25 mg of the tablet. Patients receiving 30-mg tablets should receive 25 mg of the solution (see **CLINICAL PHARMACOLOGY: Pharmacokinetics**).

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^2 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

ABILIFY[®] (aripiprazole) Oral Solution (1 mg/mL) is supplied in child-resistant bottles along with a calibrated oral dosing cup. ABILIFY oral solution is available as follows:

150-mL bottle NDC 59148-012-15

Storage

Tablets

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

Oral Solution

Store in a refrigerator at 2° C to 8° C (36° F to 46° F). Open bottles of ABILIFY oral solution should be stored in a refrigerator and can be used for up to 6 months after opening.

Tablets manufactured by Otsuka Pharmaceutical Co, Ltd, Tokyo, 101-8535 Japan or Bristol-Myers Squibb Company, Princeton, NJ 08543 USA

Oral solution manufactured by Bristol-Myers Squibb Company, Princeton, NJ 08543 USA

Distributed and marketed by Otsuka America Pharmaceutical, Inc, Rockville, MD 20850 USA

Marketed by Bristol-Myers Squibb Company, Princeton, NJ 08543 USA

US Patent Nos 4,734,416 and 5,006,528



Bristol-Myers Squibb Company



Otsuka America Pharmaceutical, Inc.

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Revised _____ 2005

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-436/S-007 & 21-713/S-004

MEDICAL REVIEW(S)

Review and Evaluation of Clinical Data
NDA #21-436

Sponsor: Otsuka/BMS
Drug: Abilify (aripiprazole) Tablets
Indications: Schizophrenia, Bipolar Mania
Material Submitted: CBE Supplement (SLR-007)
Correspondence Date: May 14, 2004
Date Received: May 18, 2004

I. Background

The sponsor is submitting this labeling supplement as "Changes Being Effected" (CBE) to add a postmarketing events section to ADVERSE REACTIONS and to update the OVERDOSAGE/Human Experience subsection of Abilify labeling.

II. CBE Labeling Changes

A. Postmarketing Events

The following new subsection has been added at the end of the ADVERSE REACTIONS section:

Other Events Observed During the Postmarketing Evaluation of Aripiprazole

Voluntary reports of adverse events in patients taking aripiprazole that have been received since market introduction and not listed above that may have no causal relationship with the drug include rare occurrences of allergic reaction (e.g., anaphylactic reaction, angioedema, laryngospasm, pruritis, or urticaria).

This new section has already been reviewed and approved as part of the NDA 21-436/S-002 application (aripiprazole for the treatment of acute bipolar mania): the 9-29-04 approval labeling for S-002 contains the above wording verbatim.

B. Overdosage Experience

The current Human Experience subsection under OVERDOSAGE has been replaced by the following language:

Human Experience

In clinical studies, accidental or intentional acute overdosage of aripiprazole was identified in patients with estimated doses up to 1080 mg with no fatalities. The reported signs and symptoms observed with aripiprazole overdose included nausea, vomiting, asthenia, diarrhea, and somnolence. In the patients who were evaluated in hospital settings, there were no reported observations indicating clinically significant adverse changes in vital signs, laboratory assessments, or ECG.

During postmarketing experience, the reported signs and symptoms observed in adult patients who overdosed with aripiprazole alone at doses up to 450 mg included tachycardia. In addition, reports of accidental overdose with aripiprazole (up to 195 mg) in children have been received. The potentially medically serious signs and symptoms reported include extrapyramidal symptoms and transient loss of consciousness with recovery.

The sponsor indicates that this updated information is supported by the most recent Six-Month Periodic Safety Update Report (PSUR) for Abilify, covering the period 17 July 2003 to 16 January 2004. This PSUR was included in this submission and the relevant section was reviewed by the undersigned.¹

III. Conclusions and Recommendations

The new postmarketing reports subsection is acceptable.

However, the revised OVERDOSAGE/Human Experience subsection cannot be completely evaluated based on the information provided by the sponsor. It appears that the sponsor intends to provide a cumulative update of human overdosage experience but, in support of this update, has provided data from only a six month period as noted above. Data from cumulative overdosage experience are required to support the sponsor's revision of this information. For

¹ Section 6.4.1 (Overdose) of the PSUR.

instance, based on a review of the submitted PSUR, I am unable to verify the sponsor's statement that non-fatal overdoses up to 1080 mg have been reported.

To describe the cumulative overdosage experience in a more complete and systematic fashion, it is recommended that the sponsor be requested to revise the language for this subsection based on their review of the cumulative safety database using a recent cut-off date for safety data and the following format:

OVERDOSAGE

Human Experience

A total of ___ cases of deliberate or accidental overdosage with aripiprazole have been reported worldwide [] These include overdoses with aripiprazole alone and in combination with other substances. []

--	--

b(4)

[] ingestion with a known outcome involved ___ mg of aripiprazole (___ times the maximum recommended daily dose) in a patient who _____ [died, recovered fully, or recovered with sequelae]. Included in the above are ___ cases of deliberate or accidental overdosage in children (age 12 and younger) involving []

Common adverse events [] with aripiprazole overdosage (alone or in combination with other substances) include _____ [list all events by COSTART term reported in at least 5% of all overdose cases]. Other clinically important signs and symptoms observed []

--	--

b(4)

In support of the revised language, it is recommended that the sponsor also submit a line listing of all overdose

cases for our review. This listing should include the following information:

- Patient identification (e.g., case number).
- Age (years).
- Amount of aripiprazole ingested (mg).
- Other substances ingested.
- Associated adverse events (by COSTART or MedDRA term).
- Outcome (fatal, fully recovered, recovered with sequelae (specify), or unknown).

Upon submission and review of an acceptable revision of this subsection and supportive line listing, this supplement may be approved.

Gregory M. Dubitsky, M.D.
October 25, 2004

cc: NDA #21-436
HFD-120 (Div. File)
HFD-120/GDubitsky
/TLaughren
/PAndreason
/TPodruchny
/SHardeman

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

/s/

Greg Dubitsky
10/25/04 08:10:19 PM
MEDICAL OFFICER

Thomas Laughren
10/26/04 10:54:55 AM
MEDICAL OFFICER

Review and Evaluation of Clinical Data
NDA #21-436

Sponsor: Otsuka/BMS
Drug: Abilify (aripiprazole) Tablets
Indications: Schizophrenia, Bipolar Mania
Material Submitted: CBE Supplement (SLR-007): Response to Approvable Letter
Correspondence Date: February 15, 2005
Date Received: February 16, 2005
Related Supplement: NDA 21-713/SLR-004 (oral solution)

I. Background

On May 14, 2004, the sponsor submitted this labeling supplement as "Changes Being Effected" (CBE) to revise Abilify labeling as follows:

- 1) add a postmarketing reports section under ADVERSE REACTIONS.
- 2) update the OVERDOSAGE/Human Experience section.

The new postmarketing reports section was reviewed and approved on 9-29-04 as part of Supplement S-002 to this NDA (aripiprazole for the treatment of acute bipolar mania).

The updated OVERDOSAGE section was reviewed by the undersigned on 10-25-04 and deemed to be unacceptable for the following reasons: 1) the supporting information was substantially deficient and did not permit a complete assessment of the proposed language and 2) the proposed language did not describe human overdose experience in a reasonably complete manner.

Accordingly, we issued an approvable letter for this supplement on 11-2-04 indicating that the postmarketing reports section had been approved and requesting further information regarding human overdose experience as well as specific text for this section of Abilify labeling.

This submission is intended to address our requests regarding human overdose experience.

II. Review of Human Overdosage Experience

A. Methodology

The sponsor searched data from clinical trials and spontaneous reports for cases involving aripiprazole overdose. Only adverse events deemed to be temporally or causally related to aripiprazole were included in analyses. Cases of accidental exposure to doses less than or equal to the highest recommended daily dose (30mg) were excluded.

Clinical Trials Data

The sponsor performed two searches of the BMS global clinical trial database with a cut-off date of 7-30-04:

- 1) a search for all cases in which overdose was reported as an adverse event term regardless of the aripiprazole dose ingested.
- 2) a search for all cases in which a daily dose of aripiprazole was greater than 60mg regardless of whether the adverse event term "overdose" was recorded.

The results of these two searches were then reconciled.

Spontaneous Reports

In addition, the BMS global safety database CARES (Corporate Adverse Events Reporting and Evaluation System) was searched for all spontaneous and literature overdose reports associated with aripiprazole for the period 7-17-02 (the International Birth Date for aripiprazole) through 7-16-04 (the most recent PSUR cut-off date).

This search was based on the following MedDRA terms: the High Level Term "Overdoses" and the preferred terms "Medication error" and "Accidental exposure."

B. Results

Clinical Trials Data

A total of 24 overdose cases were identified. Twenty-three were classified as serious.¹ None had a fatal outcome reported and all were assessed as "recovered without sequelae."

¹ Classified as serious according to 21 CFR 312.32.

Six cases reported at least one adverse event (all serious) associated with the overdose.

The amount of aripiprazole ingested ranged from 45mg to 1080mg.

No case involved a patient age 12 years or younger.

Spontaneous Reports

A total of 52 reports were retrieved, including 51 spontaneous reports and one literature report. Thirty were classified as serious. No fatalities were reported.² Outcome was reported for 20 of these cases: nine recovered, one recovered with sequelae (mydriasis and feeling abnormal), and ten were not fully recovered at the time of the report.

Thirty of the 52 reports documented at least one adverse event and 17 of the 52 involved a serious adverse event.

The amount of aripiprazole ingested ranged from 40mg to 450mg.

Ten of these cases involved children (age 12 years or younger) and the amount ingested in these cases ranged from 60mg to 195mg. Seven of these 10 cases reported at least one serious adverse event.

Adverse Events Reported with Overdose

Overdose cases were reviewed by the sponsor for adverse experiences temporally associated with aripiprazole overdose.

Serious adverse events are enumerated in Table 1 in the appendix to this review. Frequencies were computed as the percentage of the total number of overdose cases (denominator =76). For those adverse events with both serious and non-serious occurrences, the event was considered to be serious for purposes of this table. Many adverse event terms with a frequency of less than 5% were not considered to warrant inclusion in labeling for one of the following reasons:

² One spontaneous report (#12376281) describes a suicide in a patient who had been taking aripiprazole 45 mg/day prior to jumping off a bridge to her death. It seems highly unlikely that this fatal outcome was related to the large aripiprazole dose.

- considered not medically significant or not to be secondary to aripiprazole overdose.³
- insufficient data.
- same medical concept as another included term.
- overly general and non-specific.
- already described in the WARNINGS section of labeling.
- included in the diagnosis of another adverse event term.

Such events are unbolded in Table 1.

Non-serious adverse experiences are listed in a footnote to this Appendix. No non-serious event had a frequency of 5% or greater.

Medically significant adverse events possibly related to aripiprazole overdose that were reported at a frequency of 5% or more among all 76 reports were vomiting, somnolence, and tremor.

III. Revised Labeling

To describe the cumulative overdosage experience in a more complete and systematic fashion, the sponsor has revised the OVERDOSAGE/Human Experience section of labeling as follows:

OVERDOSAGE

MedDRA terminology has been used to classify the adverse events.

Human Experience

A total of 76 cases of deliberate or accidental overdosage with aripiprazole have been reported worldwide. These include overdoses with aripiprazole alone and in combination with other substances. No fatality was reported from these cases. Of the 44 cases with known outcome, 33 recovered without sequelae and one recovered with sequelae (mydriasis and feeling abnormal). The largest known acute ingestion with a known outcome involved 1080 mg of aripiprazole (36 times the maximum recommended daily dose) in a patient who fully recovered. Included in the 76 cases are 10 cases of deliberate or accidental overdosage in children (age 12 and younger) involving

³ Medically significant were those events which were either immediately life-threatening or which may jeopardize the patient or require intervention to prevent a more serious outcome.

aripiprazole ingestions up to 195 mg with no fatalities.

Common adverse events (reported in at least 5% of all overdose cases) reported with aripiprazole overdosage (alone or in combination with other substances) include vomiting, somnolence, and tremor. Other clinically important signs and symptoms observed in one or more patients with aripiprazole overdoses (alone or with other substances) include acidosis, aggression, aspartate aminotransferase increased, atrial fibrillation, bradycardia, coma, confusional state, convulsion, blood creatine phosphokinase increased, depressed level of consciousness, hypertension, hypokalemia, hypotension, lethargy, loss of consciousness, QRS complex prolonged, QT prolonged, pneumonia aspiration, respiratory arrest, status epilepticus and tachycardia.

IV. Conclusions and Recommendations

The sponsor has provided a satisfactory response to our request for additional information regarding human overdose experience. Based on the submitted data, the proposed labeling revision is acceptable.

It is recommended that this supplement, as well as the identical Supplement 004 to NDA 21-713 (for aripiprazole oral solution) be approved.

Gregory M. Dubitsky, M.D.
June 9, 2005

cc: NDA #21-436
HFD-120 (Div. File)
HFD-120/GDubitsky
/TLaughren
/PAndreason
/SHardeman

APPENDIX

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Table 1: Serious Adverse Events Associated with Aripiprazole Overdose, Frequencies and Rationale for Labeling Inclusion or Exclusion				
	Spontaneous (N=52)	Clinical Trial (N=24)	Total (N=76)	Rationale for Labeling Inclusion/Exclusion
MedDRA PT Terms^{a,b}	Count (%)	Count(%)	Count (%)	
Vomiting	3 (6)	3 (13)	6 (8)	Included as common AE
Somnolence	4 (8)	1 (4)	5 (7)	Included as common AE
Tremor	4 (8)	0	4 (5)	Included as common AE
Hypotension	3 (6)	0	3 (4)	Included-medically significant
Lethargy	2 (4)	1 (4)	3 (4)	Included-medically significant
Aspartate amino-transferase increased	2 (4)	0	2 (3)	Included-medically significant (AST 684 in one case)
Bradycardia	2 (4)	0	2 (3)	Included- medically significant
Confusional state	1 (2)	1 (4)	2 (3)	Included-medically significant
Depressed level of consciousness	2 (4)	0	2 (3)	Included-medically significant
Electrocardiogram QT prolonged	2 (4)	0	2 (3)	Included-medically significant
Fatigue	1 (2)	1 (4)	2 (3)	Excluded- not medically significant
Hypertension	2 (4)	0	2 (3)	Included-medically significant
Loss of consciousness	2 (4)	0	2 (3)	Included-medically significant
Nausea	1 (2)	1 (4)	2 (3)	Excluded- not medically significant
Respiratory rate increased	2 (4)	0	2 (3)	Excluded- data insufficient
Sedation	0	2 (8)	2 (3)	Excluded- same medical concept as somnolence

Table 1: Serious Adverse Events Associated with Aripiprazole Overdose, Frequencies and Rationale for Labeling Inclusion or Exclusion				
	Spontaneous (N=52)	Clinical Trial (N=24)	Total (N=76)	Rationale for Labeling Inclusion/Exclusion
MedDRA PT Terms^{a,b}	Count (%)	Count(%)	Count (%)	
Tachycardia^c	2 (4)	0	2 (3)	Included- medically significant
Urinary tract infection	2 (4)	0	2 (3)	Excluded- considered not related to overdose
Vision blurred^d	2 (4)	0	2 (3)	Excluded- not medically significant
Abdominal pain upper^e	1 (2)	0	1 (1)	Excluded- not medically significant
Acidosis	1 (2)	0	1 (1)	Included-medically significant
Aggression	1 (2)	0	1 (1)	Included-medically significant
Alanine aminotransferase increased	1 (2)	0	1 (1)	Excluded- not medically significant (ALT: 75 [normal: 30- 65])
Ataxia	1 (2)	0	1 (1)	Excluded- not medically significant
Atrial fibrillation	1 (2)	0	1 (1)	Included-medically significant
Blood creatine phosphokinase increased	1 (2)	0	1 (1)	Included-medically significant (CPK: 1300)
Blood glucose increased	1 (2)	0	1 (1)	Excluded- not medically significant (glucose: 121)
Blood pressure decreased	1 (2)	0	1 (1)	Excluded- not medically significant (BP slight drop)
Blunted affect	1 (2)	0	1 (1)	Excluded- not medically significant
Coma	1 (2)	0	1 (1)	Included-medically significant
Convulsion	1 (2)	0	1 (1)	Included-medically significant
Delirium	1 (2)	0	1 (1)	Excluded- part of the NMS diagnosis

Table I: Serious Adverse Events Associated with Aripiprazole Overdose, Frequencies and Rationale for Labeling Inclusion or Exclusion				
	Spontaneous (N=52)	Clinical Trial (N=24)	Total (N=76)	Rationale for Labeling Inclusion/Exclusion
MedDRA PT Terms^{a,b}	Count (%)	Count(%)	Count (%)	
Electrocardiogram QRS complex prolonged	1 (2)	0	1 (1)	Included-medically significant
Extrapyramidal disorder	1 (2)	0	1 (1)	Excluded- Data insufficient
Feeling abnormal	1 (2)	0	1 (1)	Excluded- Overly general or non-specific
Gait disturbance	1 (2)	0	1 (1)	Excluded- Overly general or non-specific
Headache	1 (2)	0	1 (1)	Excluded- not medically significant
Heart rate decreased	1 (2)	0	1 (1)	Excluded- data insufficient
Hyperhidrosis	1 (2)	0	1 (1)	Excluded- not medically significant
Hypoacusis	1 (2)	0	1 (1)	Excluded- not medically significant
Hypokalaemia	1 (2)	0	1 (1)	Included-medically significant
Musculoskeletal stiffness	1 (2)	0	1 (1)	Excluded- Overly general or non-specific
Mydriasis	1 (2)	0	1 (1)	Excluded- not medically significant
Neonatal disorder	1 (2)	0	1 (1)	Excluded- Overly general or non-specific
Nervousness	1 (2)	0	1 (1)	Excluded- not medically significant
Neuroleptic malignant syndrome	1 (2)	0	1 (1)	Excluded- already listed in the Warnings section
Pneumonia aspiration	1 (2)	0	1 (1)	Included-medically significant
Psychotic disorder	1 (2)	0	1 (1)	Excluded- Overly general or non-specific
Respiratory arrest	1 (2)	0	1 (1)	Included-medically significant

Table 1: Serious Adverse Events Associated with Aripiprazole Overdose, Frequencies and Rationale for Labeling Inclusion or Exclusion				
	Spontaneous (N=52)	Clinical Trial (N=24)	Total (N=76)	Rationale for Labeling Inclusion/Exclusion
MedDRA PT Terms^{a,b}	Count (%)	Count(%)	Count (%)	
Sluggishness	1 (2)	0	1 (1)	Excluded- not medically significant
Status epilepticus	1 (2)	0	1 (1)	Included-medically significant
Suicide attempt ^f	1 (2)	0	1 (1)	Excluded- considered not related to overdose
Tardive dyskinesia	1 (2)	0	1 (1)	Excluded- already listed in the Warnings section
White blood cell count increased	1 (2)	0	1 (1)	Excluded- not medically significant (WBC 19.7; unit unknown)

Note: Frequencies in descending order

- ^a Not included in this column are those solely non-serious events in any reports (as defined in 21CFR312.32) with a frequency less than 5%: two reports each of pruritis and speech disorder, and, one report each of the following: abnormal behaviour, anger, dysarthria, dyskinesia, emotional disorder, epistaxis, hallucination, insomnia, morbid thoughts, nipple pain, ocular hypertension, paranoia, self esteem decreased, social avoidant behaviour, social fear, thought blocking, and weight increased.
- ^b Bold terms are medically significant AEs and are included in the proposed labeling language.
- ^c Includes one case of sinus tachycardia.
- ^d Occurred in one patient with 45 mg prescribed overdose (no details) and in the other patient with 60 mg prescribed overdose with vision changed from "20/80 to 20/100."
- ^e Reported as "stomach ache" with no serious outcome reported.
- ^f While it is a medically significant event the etiology is considered more likely related to the patient's underlying disease. Details on suicide attempt was not provided. Patient with schizoaffective disorder was treated with 60 mg aripiprazole (prescribed overdose). Auditory hallucinations and delusions continued following discontinuation of aripiprazole.

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/s/

Greg Dubitsky
6/9/05 03:58:38 PM
MEDICAL OFFICER

Thomas Laughren
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