

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***

**NDA 21-436/S027**

***Trade Name:*** ABILIFY

***Generic Name:*** aripiprazole

***Sponsor:*** Otsuka Pharmaceutical Company, Ltd.

***Approval Date:*** November 19, 2009

***Indication:*** treatment of irritability associated with autistic disorder in pediatric patients (aged 6 to 17 years).

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*  
**NDA 21-436/S027**

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**CENTER FOR DRUG EVALUATION AND  
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*APPLICATION NUMBER:*  
**NDA 21-436/S027**

**APPROVAL LETTER**



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

NDA 021436/S-027

**SUPPLEMENT APPROVAL**

Otsuka Pharmaceutical Company, Ltd.  
Attention: David Goldberger, R.Ph.  
Senior Director, Regulatory Affairs  
Otsuka Pharmaceutical Development and Commercialization, Inc.  
100 Overlook Center, 1<sup>st</sup> Floor  
Princeton, NJ 08540

Dear Mr. Goldberger:

Please refer to your supplemental new drug application dated January 21, 2009, received January 21, 2009, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for ABILIFY (aripiprazole) tablets 2mg, 5mg, 10mg, 15mg, 20mg and 30mg.

We acknowledge receipt of your submissions dated May 21, 2009, August 10, 2009, September 11, 2009, October 8, 2009, October 26, 2009, November 10, 2009, and November 18, 2009.

This "Prior Approval" supplemental new drug application provides for the use of ABILIFY (aripiprazole) for the treatment of irritability associated with autistic disorder in pediatric patients (aged 6 to 17 years).

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

**CONTENT OF LABELING**

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm155657.htm> that is identical to the enclosed agreed-upon labeling text. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "**SPL for approved NDA 021436/ S-027.**"

**REQUIRED PEDIATRIC ASSESSMENTS**

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to 5 years in the treatment of irritability associated with autistic disorder because studies are highly impractical due to the low incidence of this disease state in these age ranges.

We are deferring submission of your pediatric studies for ages 6 to 16 years for the maintenance treatment of irritability associated with autistic disorder until November 21, 2014 because this product is ready for approval for use in the acute pediatric treatment of irritability associated with autistic disorder and the pediatric maintenance studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the Federal Food, Drug, and Cosmetic Act. These required studies are listed below.

1570-1            A deferred pediatric study under PREA for a maintenance treatment study to obtain long-term efficacy and safety data in patients ages 6-16 years.

Final Protocol Submission Date:	by November 21, 2010
Trial Completion Date:	by November 21, 2013
Final Report Submission:	by November 21, 2014

Submit all clinical protocols to your IND for this product. Submit all final reports to your NDA 21-436. Use the following designator to prominently label all submissions and refer to PMC set number **1570**:

**Required Pediatric Assessment(s)**

**PROMOTIONAL MATERIALS**

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert(s), at the time of initial dissemination or publication, accompanied by a Form FDA 2253. For instruction on completing the Form FDA 2253, see page 2 of the Form. For more information about submission of promotional materials to the Division of Drug Marketing, Advertising, and Communications (DDMAC), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

### **LETTERS TO HEALTH CARE PROFESSIONALS**

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

MedWatch  
Food and Drug Administration  
5600 Fishers Lane, Room 12B-05  
Rockville, MD 20857

### **MEDICATION GUIDE**

We note that ABILIFY has an issue specific (suicidality) Medication Guide. We request that you submit a comprehensive Medication Guide that incorporates all relevant safety information related to this drug to the Agency for review within six months of the date of this letter.

### **REPORTING REQUIREMENTS**

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

If you have any questions, contact CDR Kofi Ansah, Pharm.D., Senior Regulatory Project Manager, at (301)796-4158.

Sincerely,

*{See appended electronic signature page}*

Thomas Laughren, M.D.  
Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

Enclosure (Content of Labeling)

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-21436

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SUPPL-27

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OTSUKA  
PHARMACEUTICA  
L CO LTD

-----  
ABILIFY (ARIPRAZOLE)  
10/15/20/30MG

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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THOMAS P LAUGHREN  
11/19/2009

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 21-436/S027**

**LABELING**

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use ABILIFY safely and effectively. See full prescribing information for ABILIFY.

ABILIFY® (aripiprazole) Tablets

ABILIFY DISCMELT® (aripiprazole) Orally Disintegrating Tablets

ABILIFY® (aripiprazole) Oral Solution

ABILIFY® (aripiprazole) Injection FOR INTRAMUSCULAR USE ONLY

Initial U.S. Approval: 2002

**WARNINGS: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS and SUICIDALITY AND ANTIDEPRESSANT DRUGS**

*See full prescribing information for complete boxed warning.*

- Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. ABILIFY is not approved for the treatment of patients with dementia-related psychosis. (5.1)
- Children, adolescents, and young adults taking antidepressants for major depressive disorder (MDD) and other psychiatric disorders are at increased risk of suicidal thinking and behavior. (5.2)

-----RECENT MAJOR CHANGES-----

Indications and Usage, Pediatric (6 to 17 years)	
Autistic Disorder (1.4)	xx/2009
Dosage and Administration, Pediatric (6 to 17 years)	
Autistic Disorder (2.4)	xx/2009
Warnings and Precautions, Leukopenia, Neutropenia, and Agranulocytosis (5.7)	07/2009

-----INDICATIONS AND USAGE-----

ABILIFY is an atypical antipsychotic indicated as oral formulations for the:

Treatment of schizophrenia (1.1)

- Adults: Efficacy was established in four 4-6 week trials and one maintenance trial in patients with schizophrenia (14.1)
- Adolescents (ages 13-17): Efficacy was established in one 6-week trial in patients with schizophrenia (14.1)

Acute treatment of manic or mixed episodes associated with bipolar I disorder as monotherapy and as an adjunct to lithium or valproate (1.2)

- Adults: Efficacy was established in four 3-week monotherapy trials and one 6-week adjunctive trial in patients with manic or mixed episodes (14.2)
- Pediatric Patients (ages 10-17): Efficacy was established in one 4-week monotherapy trial in patients with manic or mixed episodes (14.2)

Maintenance treatment of bipolar I disorder (1.2)

- Adults: Efficacy was established in one maintenance trial (14.2)

Adjunctive treatment of major depressive disorder (MDD) (1.3)

- Adults: Efficacy was established in two 6-week trials in adults with MDD who had an inadequate response to antidepressant therapy during the current episode (14.3)

Treatment of irritability associated with autistic disorder (1.4)

- Pediatric Patients (ages 6-17 years): Efficacy was established in two 8-week trials in patients with autistic disorder (14.4)

as an injection for the:

Acute treatment of agitation associated with schizophrenia or bipolar I disorder (1.5)

- Adults: Efficacy was established in three 24-hour trials in agitated patients with schizophrenia or manic/mixed episodes of bipolar I disorder (14.5)

-----DOSAGE AND ADMINISTRATION-----

	Initial Dose	Recommended Dose	Maximum Dose
Schizophrenia – adults (2.1)	10-15 mg /day	10-15 mg /day	30 mg /day
Schizophrenia – adolescents (2.1)	2 mg/day	10 mg/day	30 mg /day
Bipolar mania – adults: monotherapy or as an adjunct to lithium or valproate (2.2)	15 mg/day	15 mg/day	30 mg /day

Bipolar mania - pediatric patients: monotherapy or as an adjunct to lithium or valproate (2.2)	2 mg/day	10 mg/day	30 mg /day
As an adjunct to antidepressants for the treatment of major depressive disorder - adults (2.3)	2-5 mg /day	5-10 mg /day	15 mg /day
Irritability associated with autistic disorder - pediatric patients (2.4)	2 mg/day	5-10 mg/day	15 mg/day
Agitation associated with schizophrenia or bipolar mania – adults (2.5)	9.75 mg /1.3 mL injected IM		30 mg/day injected IM

- Oral formulations: Administer once daily without regard to meals (2)
- IM injection: Wait at least 2 hours between doses. Maximum daily dose 30 mg (2.5)

-----DOSAGE FORMS AND STRENGTHS-----

- Tablets: 2 mg, 5 mg, 10 mg, 15 mg, 20 mg, and 30 mg (3)
- Orally Disintegrating Tablets: 10 mg and 15 mg (3)
- Oral Solution: 1 mg/mL (3)
- Injection: 9.75 mg/1.3 mL single-dose vial (3)

-----CONTRAINDICATIONS-----

Known hypersensitivity to ABILIFY (4)

-----WARNINGS AND PRECAUTIONS-----

- *Elderly Patients with Dementia-Related Psychosis* Increased incidence of cerebrovascular adverse events (eg, stroke, transient ischemic attack, including fatalities) (5.1)
- *Suicidality and Antidepressants* Increased risk of suicidality in children, adolescents, and young adults with major depressive disorder (5.2)
- *Neuroleptic Malignant Syndrome* Manage with immediate discontinuation and close monitoring (5.3)
- *Tardive Dyskinesia* Discontinue if clinically appropriate (5.4)
- *Hyperglycemia and Diabetes Mellitus* Monitor glucose regularly in patients with and at risk for diabetes (5.5)
- *Orthostatic Hypotension* Use with caution in patients with known cardiovascular or cerebrovascular disease (5.6)
- *Leukopenia, Neutropenia, and Agranulocytosis* have been reported with antipsychotics including ABILIFY. Patients with a history of a clinically significant low white blood cell count (WBC) or a drug-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of ABILIFY should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors (5.7)
- *Seizures/Convulsions* Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold (5.8)
- *Potential for Cognitive and Motor Impairment* Use caution when operating machinery (5.9)
- *Suicide* The possibility of a suicide attempt is inherent in schizophrenia and bipolar disorder. Closely supervise high-risk patients (5.11)

-----ADVERSE REACTIONS-----

Commonly observed adverse reactions (incidence ≥5% and at least twice that for placebo) were (6.2):

- Adult patients with schizophrenia: akathisia
- Pediatric patients (13 to 17 years) with schizophrenia: extrapyramidal disorder, somnolence, and tremor
- Adult patients (monotherapy) with bipolar mania: akathisia, sedation, restlessness, tremor, and extrapyramidal disorder
- Adult patients (adjunctive therapy with lithium or valproate) with bipolar mania: akathisia, insomnia, and extrapyramidal disorder
- Pediatric patients (10 to 17 years) with bipolar mania: somnolence, extrapyramidal disorder, fatigue, nausea, akathisia, blurred vision, salivary hypersecretion, and dizziness
- Adult patients with major depressive disorder (adjunctive treatment to antidepressant therapy): akathisia, restlessness, insomnia, constipation, fatigue, and blurred vision
- Pediatric patients (6 to 17 years) with autistic disorder: sedation, fatigue, vomiting, somnolence, tremor, pyrexia, drooling, decreased appetite, salivary hypersecretion, extrapyramidal disorder, and lethargy
- Adult patients with agitation associated with schizophrenia or bipolar mania: nausea.

To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-800-721-5072 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch)

-----DRUG INTERACTIONS-----

- Strong CYP3A4 (eg, ketoconazole) or CYP2D6 (eg, fluoxetine) inhibitors will increase ABILIFY drug concentrations; reduce ABILIFY dose by one-

half when used concomitantly (2.6, 7.1), except when used as adjunctive treatment with antidepressants (2.6)

- CYP3A4 inducers (eg, carbamazepine) will decrease ABILIFY drug concentrations; double ABILIFY dose when used concomitantly (2.6, 7.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: XX/2009

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### **WARNINGS: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS and SUICIDALITY AND ANTIDEPRESSANT DRUGS**

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. ABILIFY (aripiprazole) is not approved for the treatment of patients with dementia-related psychosis [*see WARNINGS AND PRECAUTIONS (5.1)*].

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of adjunctive ABILIFY or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. ABILIFY is not approved for use in pediatric patients with depression [*see WARNINGS AND PRECAUTIONS (5.2)*].

# **1 INDICATIONS AND USAGE**

## **1.1 Schizophrenia**

ABILIFY is indicated for the treatment of schizophrenia. The efficacy of ABILIFY was established in four 4-6 week trials in adults and one 6-week trial in adolescents (13-17 years). Maintenance efficacy was demonstrated in one trial in adults and can be extrapolated to adolescents [*see CLINICAL STUDIES (14.1)*].

## **1.2 Bipolar I Disorder**

### **Monotherapy**

ABILIFY is indicated for the acute and maintenance treatment of manic and mixed episodes associated with bipolar I disorder. Efficacy was established in four 3-week monotherapy trials in adults and one 4-week monotherapy trial in pediatric patients (10-17 years). Maintenance efficacy was demonstrated in a monotherapy trial in adults and can be extrapolated to pediatric patients (10-17 years) [*see CLINICAL STUDIES (14.2)*].

### **Adjunctive Therapy**

ABILIFY is indicated as an adjunctive therapy to either lithium or valproate for the acute treatment of manic and mixed episodes associated with bipolar I disorder. Efficacy was established in one 6-week adjunctive trial in adults and can be extrapolated to pediatric patients (10-17 years) [*see CLINICAL STUDIES (14.2)*].

## **1.3 Adjunctive Treatment of Major Depressive Disorder**

ABILIFY is indicated for use as an adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD). Efficacy was established in two 6-week trials in adults with MDD who had an inadequate response to antidepressant therapy during the current episode. [*see CLINICAL STUDIES (14.3)*].

## **1.4 Irritability Associated with Autistic Disorder**

ABILIFY is indicated for the treatment of irritability associated with autistic disorder. Efficacy was established in two 8-week trials in pediatric patients (aged 6 to 17 years) with irritability associated with autistic disorder (including symptoms of aggression

towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods) [see *CLINICAL STUDIES (14.4)*].

## **1.5 Agitation Associated with Schizophrenia or Bipolar I Mania**

ABILIFY Injection is indicated for the acute treatment of agitation associated with schizophrenia or bipolar disorder, manic or mixed. "Psychomotor agitation" is defined in DSM-IV as "excessive motor activity associated with a feeling of inner tension". Patients experiencing agitation often manifest behaviors that interfere with their diagnosis and care (eg, threatening behaviors, escalating or urgently distressing behavior, or self-exhausting behavior), leading clinicians to the use of intramuscular antipsychotic medications to achieve immediate control of the agitation. Efficacy was established in three short-term (24-hour) trials in adults [see *CLINICAL STUDIES (14.5)*].

## **1.6 Special Considerations in Treating Pediatric Schizophrenia, Bipolar I Disorder, and Irritability Associated with Autistic Disorder**

Psychiatric disorders in children and adolescents are often serious mental disorders with variable symptom profiles that are not always congruent with adult diagnostic criteria. It is recommended that psychotropic medication therapy for pediatric patients only be initiated after a thorough diagnostic evaluation has been conducted and careful consideration given to the risks associated with medication treatment. Medication treatment for pediatric patients with schizophrenia, bipolar I disorder, and irritability associated with autistic disorder is indicated as part of a total treatment program that often includes psychological, educational, and social interventions.

## **2 DOSAGE AND ADMINISTRATION**

### **2.1 Schizophrenia**

#### ***Adults***

Dose Selection—The recommended starting and target dose for ABILIFY is 10 mg/day 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 mg/day to 30 mg/day, when administered as the tablet formulation; however, doses higher than 10 mg/day or 15 mg/day were not more effective than 10 mg/day or 15 mg/day. Dosage

increases should generally not be made before 2 weeks, the time needed to achieve steady-state [see *CLINICAL STUDIES (14.1)*].

**Maintenance Treatment**—Maintenance of efficacy in schizophrenia was demonstrated in a trial involving patients with schizophrenia who had been symptomatically stable on other antipsychotic medications for periods of 3 months or longer. These patients were discontinued from those medications and randomized to either ABILIFY 15 mg/day or placebo, and observed for relapse [see *CLINICAL STUDIES (14.1)*]. Patients should be periodically reassessed to determine the continued need for maintenance treatment.

### **Adolescents**

**Dose Selection**—The recommended target dose of ABILIFY is 10 mg/day. Aripiprazole was studied in adolescent patients 13 to 17 years of age with schizophrenia at daily doses of 10 mg and 30 mg. The starting daily dose of the tablet formulation in these patients was 2 mg, which was titrated to 5 mg after 2 days and to the target dose of 10 mg after 2 additional days. Subsequent dose increases should be administered in 5 mg increments. The 30 mg/day dose was not shown to be more efficacious than the 10 mg/day dose. ABILIFY can be administered without regard to meals [see *CLINICAL STUDIES (14.1)*].

**Maintenance Treatment**—The efficacy of ABILIFY for the maintenance treatment of schizophrenia in the adolescent population has not been evaluated. While there is no body of evidence available to answer the question of how long the adolescent patient treated with ABILIFY should be maintained on the drug, maintenance efficacy can be extrapolated from adult data along with comparisons of aripiprazole pharmacokinetic parameters in adult and pediatric patients. Thus, it is generally recommended that responding patients be continued beyond the acute response, but at the lowest dose needed to maintain remission. 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.

## 2.2 Bipolar I Disorder

### **Adults**

Dose Selection—The recommended starting and target dose is 15 mg given once daily as monotherapy or as adjunctive therapy with lithium or valproate. ABILIFY may be given without regard to meals. The dose may be increased to 30 mg/day based on clinical response. The safety of doses above 30 mg/day has not been evaluated in clinical trials [see *CLINICAL STUDIES (14.2)*].

Maintenance Treatment—Maintenance of efficacy in bipolar I disorder was demonstrated in a trial involving patients who had been symptomatically stable on ABILIFY Tablets (15 mg/day or 30 mg/day, as monotherapy) for at least 6 consecutive weeks. These patients were discontinued from those medications and randomized to either ABILIFY, at the same dose they were stabilized on, or placebo, and observed for relapse [see *CLINICAL STUDIES (14.2)*]. Patients should be periodically reassessed to determine the continued need for maintenance treatment.

### **Pediatric Patients**

Dose Selection—The efficacy of ABILIFY has been established in the treatment of pediatric patients 10 to 17 years of age with bipolar I disorder at doses of 10 mg/day or 30 mg/day. The recommended target dose of ABILIFY is 10 mg/day, as monotherapy or as adjunctive therapy with lithium or valproate. The starting daily dose of the tablet formulation in these patients was 2 mg/day, which was titrated to 5 mg/day after 2 days and to the target dose of 10 mg/day after 2 additional days. Subsequent dose increases should be administered in 5 mg/day increments. ABILIFY can be administered without regard to meals. [See *CLINICAL STUDIES (14.2)*.]

Maintenance Treatment—The efficacy of ABILIFY for the maintenance treatment of bipolar I disorder in the pediatric population has not been evaluated. While there is no body of evidence available to answer the question of how long the pediatric patient treated with ABILIFY should be maintained, maintenance efficacy can be extrapolated from adult data along with comparisons of aripiprazole pharmacokinetic parameters in adult and pediatric patients. Thus, responding patients may be considered for continued treatment beyond the acute response at the lowest dose required to maintain remission. Patients should be periodically reassessed to determine the continued need for maintenance treatment.

## **2.3 Adjunctive Treatment of Major Depressive Disorder**

### ***Adults***

Dose Selection—The recommended starting dose for ABILIFY as adjunctive treatment for patients already taking an antidepressant is 2 mg/day to 5 mg/day. The efficacy of ABILIFY as an adjunctive therapy for major depressive disorder was established within a dose range of 2 mg/day to 15 mg/day. Dose adjustments of up to 5 mg/day should occur gradually, at intervals of no less than 1 week [*see CLINICAL STUDIES (14.3)*].

Maintenance Treatment—The efficacy of ABILIFY for the adjunctive maintenance treatment of major depressive disorder has not been evaluated. While there is no body of evidence available to answer the question of how long the patient treated with ABILIFY should be maintained, patients should be periodically reassessed to determine the continued need for maintenance treatment.

## **2.4 Irritability Associated with Autistic Disorder**

### ***Pediatric Patients***

Dose Selection—The efficacy of aripiprazole has been established in the treatment of pediatric patients 6 to 17 years of age with irritability associated with autistic disorder at doses of 5 mg/day to 15 mg/day. The dosage of ABILIFY should be individualized according to tolerability and response.

Dosing should be initiated at 2 mg/day. The dose should be increased to 5 mg/day, with subsequent increases to 10 mg/day or 15 mg/day if needed. Dose adjustments of up to 5 mg/day should occur gradually, at intervals of no less than 1 week [*see CLINICAL STUDIES (14.4)*].

Maintenance Treatment—The efficacy of ABILIFY for the maintenance treatment of irritability associated with autistic disorder has not been evaluated. While there is no body of evidence available to answer the question of how long the patient treated with ABILIFY should be maintained, patients should be periodically reassessed to determine the continued need for maintenance treatment.

## 2.5 Agitation Associated with Schizophrenia or Bipolar Mania (Intramuscular Injection)

### Adults

Dose Selection—The recommended dose in these patients is 9.75 mg. The effectiveness of aripiprazole injection in controlling agitation in schizophrenia and bipolar mania was demonstrated over a dose range of 5.25 mg to 15 mg. No additional benefit was demonstrated for 15 mg compared to 9.75 mg. A lower dose of 5.25 mg may be considered when clinical factors warrant. If agitation warranting a second dose persists following the initial dose, cumulative doses up to a total of 30 mg/day may be given. However, the efficacy of repeated doses of aripiprazole injection in agitated patients has not been systematically evaluated in controlled clinical trials. The safety of total daily doses greater than 30 mg or injections given more frequently than every 2 hours have not been adequately evaluated in clinical trials [see *CLINICAL STUDIES (14.5)*].

If ongoing aripiprazole therapy is clinically indicated, oral aripiprazole in a range of 10 mg/day to 30 mg/day should replace aripiprazole injection as soon as possible [see *DOSAGE AND ADMINISTRATION (2.1 and 2.2)*].

### Administration of ABILIFY Injection

To administer ABILIFY Injection, draw up the required volume of solution into the syringe as shown in Table 1. Discard any unused portion.

**Table 1: ABILIFY Injection Dosing Recommendations**

Single-Dose	Required Volume of Solution
5.25 mg	0.7 mL
9.75 mg	1.3 mL
15 mg	2 mL

ABILIFY Injection is intended for intramuscular use only. Do not administer intravenously or subcutaneously. Inject slowly, deep into the muscle mass.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

## 2.6 Dosage Adjustment

Dosage adjustments in adults are not routinely indicated on the basis of age, gender, race, or renal or hepatic impairment status [*see USE IN SPECIFIC POPULATIONS (8.4-8.10)*].

*Dosage adjustment for patients taking aripiprazole concomitantly with strong CYP3A4 inhibitors:* When concomitant administration of aripiprazole with strong CYP3A4 inhibitors such as ketoconazole or clarithromycin is indicated, the aripiprazole dose should be reduced to one-half the usual dose. When the CYP3A4 inhibitor is withdrawn from the combination therapy, the aripiprazole dose should then be increased [*see DRUG INTERACTIONS (7.1)*].

*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, the aripiprazole dose should then be increased [*see DRUG INTERACTIONS (7.1)*]. When adjunctive ABILIFY is administered to patients with major depressive disorder, ABILIFY should be administered without dosage adjustment as specified in *DOSAGE AND ADMINISTRATION (2.3)*.

*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. Additional dose increases should be based on clinical evaluation. When the CYP3A4 inducer is withdrawn from the combination therapy, the aripiprazole dose should be reduced to 10 mg to 15 mg [*see DRUG INTERACTIONS (7.1)*].

## 2.7 Dosing of Oral Solution

The oral solution can be substituted for tablets on a mg-per-mg basis up to the 25 mg dose level. Patients receiving 30 mg tablets should receive 25 mg of the solution [*see CLINICAL PHARMACOLOGY (12.3)*].

## 2.8 Dosing of Orally Disintegrating Tablets

The dosing for ABILIFY Orally Disintegrating Tablets is the same as for the oral tablets [see *DOSAGE AND ADMINISTRATION* (2.1, 2.2, 2.3, and 2.4)].

## 3 DOSAGE FORMS AND STRENGTHS

ABILIFY<sup>®</sup> (aripiprazole) Tablets are available as described in Table 2.

**Table 2: ABILIFY Tablet Presentations**

<b>Tablet Strength</b>	<b>Tablet Color/Shape</b>	<b>Tablet Markings</b>
2 mg	green modified rectangle	"A-006" and "2"
5 mg	blue modified rectangle	"A-007" and "5"
10 mg	pink modified rectangle	"A-008" and "10"
15 mg	yellow round	"A-009" and "15"
20 mg	white round	"A-010" and "20"
30 mg	pink round	"A-011" and "30"

ABILIFY DISCMELT<sup>®</sup> (aripiprazole) Orally Disintegrating Tablets are available as described in Table 3.

**Table 3: ABILIFY DISCMELT Orally Disintegrating Tablet Presentations**

<b>Tablet Strength</b>	<b>Tablet Color/Shape</b>	<b>Tablet Markings</b>
10 mg	pink (with scattered specks) round	"A" and "640" "10"
15 mg	yellow (with scattered specks) round	"A" and "641" "15"

ABILIFY<sup>®</sup> (aripiprazole) Oral Solution (1 mg/mL) is a clear, colorless to light yellow solution, supplied in child-resistant bottles along with a calibrated oral dosing cup.

ABILIFY<sup>®</sup> (aripiprazole) Injection for Intramuscular Use is a clear, colorless solution available as a ready-to-use, 9.75 mg/1.3 mL (7.5 mg/mL) solution in clear, Type 1 glass vials.

## 4 CONTRAINDICATIONS

Known hypersensitivity reaction to ABILIFY. Reactions have ranged from pruritus/urticaria to anaphylaxis [*see ADVERSE REACTIONS (6.3)*].

## 5 WARNINGS AND PRECAUTIONS

### 5.1 Use in Elderly Patients with Dementia-Related Psychosis

#### Increased Mortality

**Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. ABILIFY (aripiprazole) is not approved for the treatment of patients with dementia-related psychosis [*see BOXED WARNING*].**

#### Cerebrovascular Adverse Events, Including Stroke

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 BOXED WARNING*].

#### ***Safety Experience in Elderly Patients with Psychosis Associated with Alzheimer's Disease***

In three, 10-week, placebo-controlled studies of aripiprazole in elderly patients with psychosis associated with Alzheimer's disease (n=938; mean age: 82.4 years; range: 56-99 years), the treatment-emergent adverse events that were reported at an incidence of  $\geq 3\%$  and aripiprazole incidence at least twice that for placebo were lethargy [placebo 2%, aripiprazole 5%], somnolence (including sedation) [placebo 3%, aripiprazole 8%], and incontinence (primarily, urinary incontinence) [placebo 1%, aripiprazole 5%], excessive salivation [placebo 0%, aripiprazole 4%], and lightheadedness [placebo 1%, aripiprazole 4%].

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 BOXED WARNING*].

## **5.2 Clinical Worsening of Depression and Suicide Risk**

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with MDD and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, Obsessive Compulsive Disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 4.

**Table 4:**

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated
	<b>Increases Compared to Placebo</b>
<18	14 additional cases
18-24	5 additional cases
	<b>Decreases Compared to Placebo</b>
25-64	1 fewer case
≥65	6 fewer cases

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, ie, beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

**All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.**

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for MDD as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

**Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers. Such monitoring should include daily observation by families and caregivers.** Prescriptions for ABILIFY should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

**Screening Patients for Bipolar Disorder:** A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression.

It should be noted that ABILIFY is not approved for use in treating depression in the pediatric population.

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

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) may occur with administration of antipsychotic drugs, including aripiprazole. Rare cases of NMS occurred during aripiprazole treatment in the 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) 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.

## **5.4 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.

## **5.5 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 [*see ADVERSE REACTIONS (6.2, 6.3)*]. 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.

## 5.6 Orthostatic Hypotension

Aripiprazole may cause orthostatic hypotension, perhaps due to its  $\alpha_1$ -adrenergic receptor antagonism. The incidence of orthostatic hypotension-associated events from short-term, placebo-controlled trials of adult patients on oral ABILIFY (n=2467) included (aripiprazole incidence, placebo incidence) orthostatic hypotension (1%, 0.3%), postural dizziness (0.5%, 0.3%), and syncope (0.5%, 0.4%); of pediatric patients 6 to 17 years of age (n=611) on oral ABILIFY included orthostatic hypotension (0.5%, 0%), postural dizziness (0.3%, 0%), and syncope (0.2%, 0%); and of patients on ABILIFY Injection (n=501) included orthostatic hypotension (0.6%, 0%), postural dizziness (0.2%, 0.5%), and syncope (0.4%, 0%).

The incidence of a significant orthostatic change in blood pressure (defined as a decrease in systolic blood pressure  $\geq 20$  mmHg accompanied by an increase in heart rate  $\geq 25$  when comparing standing to supine values) for aripiprazole was not meaningfully different from placebo (aripiprazole incidence, placebo incidence): in adult oral aripiprazole-treated patients (4%, 2%), in pediatric oral aripiprazole-treated patients aged 6 to 17 years (0.2%, 1%), or in aripiprazole injection-treated patients (3%, 2%).

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).

If parenteral benzodiazepine therapy is deemed necessary in addition to aripiprazole injection treatment, patients should be monitored for excessive sedation and for orthostatic hypotension [*see DRUG INTERACTIONS (7.3)*].

## 5.7 Leukopenia, Neutropenia, and Agranulocytosis

*Class Effect:* In clinical trial and/or postmarketing experience, events of leukopenia/neutropenia have been reported temporally related to antipsychotic agents, including ABILIFY. Agranulocytosis has also been reported.

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) and history of drug-induced leukopenia/neutropenia. Patients with a history of a clinically significant low WBC or drug-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of

therapy and discontinuation of ABILIFY should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count  $<1000/\text{mm}^3$ ) should discontinue ABILIFY and have their WBC followed until recovery.

## **5.8 Seizures/Convulsions**

In short-term, placebo-controlled trials, seizures/convulsions occurred in 0.1% (3/2467) of adult patients treated with oral aripiprazole, in 0.2% (1/611) of pediatric patients (6 to 17 years), and in 0.2% (1/501) of adult aripiprazole injection-treated patients.

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.

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

ABILIFY, like other antipsychotics, may have the potential to impair judgment, thinking, or motor skills. For example, in short-term, placebo-controlled trials, somnolence (including sedation) was reported as follows (aripiprazole incidence, placebo incidence): in adult patients (n=2467) treated with oral ABILIFY (11%, 6%), in pediatric patients ages 6 to 17 (n=611) (24%, 6%), and in adult patients (n=501) on ABILIFY Injection (9%, 6%). Somnolence (including sedation) led to discontinuation in 0.3% (8/2467) of adult patients and 3% (15/611) of pediatric patients (6 to 17 years) on oral ABILIFY in short-term, placebo-controlled trials, but did not lead to discontinuation of any adult patients on ABILIFY Injection.

Despite the relatively modest increased incidence of these events compared to placebo, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that therapy with ABILIFY does not affect them adversely.

## **5.10 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) [see *ADVERSE REACTIONS (6.3)*].

## **5.11 Suicide**

The possibility of a suicide attempt is inherent in psychotic illnesses, bipolar disorder, and major depressive 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 [see *ADVERSE REACTIONS (6.2, 6.3)*].

In two 6-week placebo-controlled studies of aripiprazole as adjunctive treatment of major depressive disorder, the incidences of suicidal ideation and suicide attempts were 0% (0/371) for aripiprazole and 0.5% (2/366) for placebo.

## **5.12 Dysphagia**

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use, including ABILIFY. 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 *WARNINGS AND PRECAUTIONS (5.1) and ADVERSE REACTIONS (6.3)*].

## **5.13 Use in Patients with Concomitant Illness**

Clinical experience with ABILIFY in patients with certain concomitant systemic illnesses is limited [see *USE IN SPECIFIC POPULATIONS (8.6, 8.7)*].

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 [see *WARNINGS AND PRECAUTIONS (5.1, 5.6)*].

## 6 ADVERSE REACTIONS

### 6.1 Overall Adverse Reactions Profile

The following are discussed in more detail in other sections of the labeling:

- Use in Elderly Patients with Dementia-Related Psychosis [*see BOXED WARNING and WARNINGS AND PRECAUTIONS (5.1)*]
- Clinical Worsening of Depression and Suicide Risk [*see BOXED WARNING and WARNINGS AND PRECAUTIONS (5.2)*]
- Neuroleptic Malignant Syndrome (NMS) [*see WARNINGS AND PRECAUTIONS (5.3)*]
- Tardive Dyskinesia [*see WARNINGS AND PRECAUTIONS (5.4)*]
- Hyperglycemia and Diabetes Mellitus [*see WARNINGS AND PRECAUTIONS (5.5)*]
- Orthostatic Hypotension [*see WARNINGS AND PRECAUTIONS (5.6)*]
- Leukopenia, Neutropenia, and Agranulocytosis [*see WARNINGS AND PRECAUTIONS (5.7)*]
- Seizures/Convulsions [*see WARNINGS AND PRECAUTIONS (5.8)*]
- Potential for Cognitive and Motor Impairment [*see WARNINGS AND PRECAUTIONS (5.9)*]
- Body Temperature Regulation [*see WARNINGS AND PRECAUTIONS (5.10)*]
- Suicide [*see WARNINGS AND PRECAUTIONS (5.11)*]
- Dysphagia [*see WARNINGS AND PRECAUTIONS (5.12)*]
- Use in Patients with Concomitant Illness [*see WARNINGS AND PRECAUTIONS (5.13)*]

The most common adverse reactions in adult patients in clinical trials ( $\geq 10\%$ ) were nausea, vomiting, constipation, headache, dizziness, akathisia, anxiety, insomnia, and restlessness.

The most common adverse reactions in the pediatric clinical trials ( $\geq 10\%$ ) were somnolence, headache, vomiting, extrapyramidal disorder, fatigue, increased appetite, insomnia, nausea, nasopharyngitis, and weight increased.

Aripiprazole has been evaluated for safety in 13,543 adult patients who participated in multiple-dose, clinical trials in schizophrenia, bipolar disorder, major depressive disorder, Dementia of the Alzheimer's type, Parkinson's disease, and alcoholism, and who had approximately 7619 patient-years of exposure to oral aripiprazole and 749 patients with exposure to aripiprazole injection. A total of 3390 patients were treated with oral aripiprazole for at least 180 days and 1933 patients treated with oral aripiprazole had at least 1 year of exposure.

Aripiprazole has been evaluated for safety in 920 patients (6 to 17 years) who participated in multiple-dose, clinical trials in schizophrenia, bipolar mania, or autistic disorder and who had approximately 517 patient-years of exposure to oral aripiprazole. A total of 465 pediatric patients were treated with oral aripiprazole for at least 180 days and 117 pediatric patients treated with oral aripiprazole had at least 1 year of exposure.

The conditions and duration of treatment with aripiprazole (monotherapy and adjunctive therapy with antidepressants or mood stabilizers) 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, MedDRA dictionary terminology has been used 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 reactions 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 events meeting the defined criteria, regardless of investigator causality are included.

Throughout this section, adverse reactions are reported. These are adverse events that were considered to be reasonably associated with the use of ABILIFY (adverse drug

reactions) based on the comprehensive assessment of the available adverse event information. A causal association for ABILIFY often cannot be reliably established in individual cases.

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 prescriber with some basis for estimating the relative contribution of drug and nondrug factors to the adverse reaction incidence in the population studied.

## **6.2 Clinical Studies Experience**

### **Adult 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 oral aripiprazole was administered in doses ranging from 2 mg/day to 30 mg/day.

#### *Adverse Reactions Associated with Discontinuation of Treatment*

Overall, there was little difference in the incidence of discontinuation due to adverse reactions between aripiprazole-treated (7%) and placebo-treated (9%) patients. The types of adverse reactions that led to discontinuation were similar for the aripiprazole-treated and placebo-treated patients.

#### *Commonly Observed Adverse Reactions*

The only commonly observed adverse reaction associated with the use of aripiprazole in patients with schizophrenia (incidence of 5% or greater and aripiprazole incidence at least twice that for placebo) was akathisia (aripiprazole 8%; placebo 4%).

## Adult Patients with Bipolar Mania

### *Monotherapy*

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

#### *Adverse Reactions Associated with Discontinuation of Treatment*

Overall, in patients with bipolar mania, there was little difference in the incidence of discontinuation due to adverse reactions between aripiprazole-treated (11%) and placebo-treated (10%) patients. The types of adverse reactions that led to discontinuation were similar between the aripiprazole-treated and placebo-treated patients.

#### *Commonly Observed Adverse Reactions*

Commonly observed adverse reactions 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 5.

**Table 5: Commonly Observed Adverse Reactions in Short-Term, Placebo-Controlled Trials of Adult Patients with Bipolar Mania Treated with Oral ABILIFY Monotherapy**

Preferred Term	Percentage of Patients Reporting Reaction	
	Aripiprazole (n=917)	Placebo (n=753)
Akathisia	13	4
Sedation	8	3
Restlessness	6	3
Tremor	6	3
Extrapyramidal Disorder	5	2

#### **Less Common Adverse Reactions in Adults**

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

**Table 6: Adverse Reactions in Short-Term, Placebo-Controlled Trials in Adult Patients Treated with Oral ABILIFY**

System Organ Class Preferred Term	Percentage of Patients Reporting Reaction <sup>a</sup>	
	Aripiprazole (n=1843)	Placebo (n=1166)
<b>Eye Disorders</b>		
Blurred Vision	3	1
<b>Gastrointestinal Disorders</b>		
Nausea	15	11
Constipation	11	7
Vomiting	11	6
Dyspepsia	9	7
Dry Mouth	5	4
Toothache	4	3
Abdominal Discomfort	3	2
Stomach Discomfort	3	2
<b>General Disorders and Administration Site Conditions</b>		
Fatigue	6	4
Pain	3	2
<b>Musculoskeletal and Connective Tissue Disorders</b>		
Musculoskeletal Stiffness	4	3
Pain in Extremity	4	2
Myalgia	2	1
Muscle Spasms	2	1
<b>Nervous System Disorders</b>		
Headache	27	23
Dizziness	10	7
Akathisia	10	4
Sedation	7	4
Extrapyramidal Disorder	5	3
Tremor	5	3
Somnolence	5	3
<b>Psychiatric Disorders</b>		
Agitation	19	17
Insomnia	18	13
Anxiety	17	13
Restlessness	5	3
<b>Respiratory, Thoracic, and Mediastinal Disorders</b>		
Pharyngolaryngeal Pain	3	2
Cough	3	2

<sup>a</sup> Adverse reactions reported by at least 2% of patients treated with oral aripiprazole, except adverse reactions which had an incidence equal to or less than placebo.

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

## **Adult Patients with Adjunctive Therapy with Bipolar Mania**

The following findings are based on a placebo-controlled trial of adult patients with bipolar disorder in which aripiprazole was administered at doses of 15 mg/day or 30 mg/day as adjunctive therapy with lithium or valproate.

### *Adverse Reactions Associated with Discontinuation of Treatment*

In a study of patients who were already tolerating either lithium or valproate as monotherapy, discontinuation rates due to adverse reactions were 12% for patients treated with adjunctive aripiprazole compared to 6% for patients treated with adjunctive placebo. The most common adverse drug reactions associated with discontinuation in the adjunctive aripiprazole-treated compared to placebo-treated patients were akathisia (5% and 1%, respectively) and tremor (2% and 1%, respectively).

### *Commonly Observed Adverse Reactions*

The commonly observed adverse reactions associated with adjunctive aripiprazole and lithium or valproate in patients with bipolar mania (incidence of 5% or greater and incidence at least twice that for adjunctive placebo) were: akathisia, insomnia, and extrapyramidal disorder.

## **Less Common Adverse Reactions in Adult Patients with Adjunctive Therapy in Bipolar Mania**

Table 7 enumerates the incidence, rounded to the nearest percent, of adverse reactions that occurred during acute treatment (up to 6 weeks), including only those reactions that occurred in 2% or more of patients treated with adjunctive aripiprazole (doses of 15 mg/day or 30 mg/day) and lithium or valproate and for which the incidence in patients treated with this combination was greater than the incidence in patients treated with placebo plus lithium or valproate.

**Table 7: Adverse Reactions in a Short-Term, Placebo-Controlled Trial of Adjunctive Therapy in Patients with Bipolar Disorder**

System Organ Class Preferred Term	Percentage of Patients Reporting Reaction <sup>a</sup>	
	Aripiprazole + Li or Val* (n=253)	Placebo + Li or Val* (n=130)
<b>Gastrointestinal Disorders</b>		
Nausea	8	5
Vomiting	4	0
Salivary Hypersecretion	4	2
Dry Mouth	2	1
<b>Infections and Infestations</b>		
Nasopharyngitis	3	2
<b>Investigations</b>		
Weight Increased	2	1
<b>Nervous System Disorders</b>		
Akathisia	19	5
Tremor	9	6
Extrapyramidal Disorder	5	1
Dizziness	4	1
Sedation	4	2
<b>Psychiatric Disorders</b>		
Insomnia	8	4
Anxiety	4	1
Restlessness	2	1

<sup>a</sup> Adverse reactions reported by at least 2% of patients treated with oral aripiprazole, except adverse reactions which had an incidence equal to or less than placebo.

\* Lithium or Valproate

### **Pediatric Patients (13 to 17 years) with Schizophrenia**

The following findings are based on one 6-week placebo-controlled trial in which oral aripiprazole was administered in doses ranging from 2 mg/day to 30 mg/day.

#### *Adverse Reactions Associated with Discontinuation of Treatment*

The incidence of discontinuation due to adverse reactions between aripiprazole-treated and placebo-treated pediatric patients (13 to 17 years) was 5% and 2%, respectively.

### *Commonly Observed Adverse Reactions*

Commonly observed adverse reactions associated with the use of aripiprazole in adolescent patients with schizophrenia (incidence of 5% or greater and aripiprazole incidence at least twice that for placebo) were extrapyramidal disorder, somnolence, and tremor.

### **Pediatric Patients (10 to 17 years) with Bipolar Mania**

The following findings are based on one 4-week placebo-controlled trial in which oral aripiprazole was administered in doses of 10 mg/day or 30 mg/day.

### *Adverse Reactions Associated with Discontinuation of Treatment*

The incidence of discontinuation due to adverse reactions between aripiprazole-treated and placebo-treated pediatric patients (10 to 17 years) was 7% and 2%, respectively.

### *Commonly Observed Adverse Reactions*

Commonly observed adverse reactions associated with the use of aripiprazole in pediatric patients with bipolar mania (incidence of 5% or greater and aripiprazole incidence at least twice that for placebo) are shown in Table 8.

**Table 8: Commonly Observed Adverse Reactions in Short-Term, Placebo-Controlled Trials of Pediatric Patients (10 to 17 years) with Bipolar Mania Treated with Oral ABILIFY**

<b>Preferred Term</b>	<b>Percentage of Patients Reporting Reaction</b>	
	<b>Aripiprazole (n=197)</b>	<b>Placebo (n=97)</b>
Somnolence	23	3
Extrapyramidal Disorder	20	3
Fatigue	11	4
Nausea	11	4
Akathisia	10	2
Blurred Vision	8	0
Salivary Hypersecretion	6	0
Dizziness	5	1

## Pediatric Patients (6 to 17 years) with Autistic Disorder

The following findings are based on two 8-week, placebo-controlled trials in which oral aripiprazole was administered in doses of 2 mg/day to 15 mg/day.

### *Adverse Reactions Associated with Discontinuation of Treatment*

The incidence of discontinuation due to adverse reactions between aripiprazole-treated and placebo-treated pediatric patients (6 to 17 years) was 10% and 8%, respectively.

### *Commonly Observed Adverse Reactions*

Commonly observed adverse reactions associated with the use of aripiprazole in pediatric patients with autistic disorder (incidence of 5% or greater and aripiprazole incidence at least twice that for placebo) are shown in Table 9.

**Table 9: Commonly Observed Adverse Reactions in Short-Term, Placebo-Controlled Trials of Pediatric Patients (6 to 17 years) with Autistic Disorder Treated with Oral ABILIFY**

Preferred Term	Percentage of Patients Reporting Reaction	
	Aripiprazole (n=212)	Placebo (n=101)
Sedation	21	4
Fatigue	17	2
Vomiting	14	7
Somnolence	10	4
Tremor	10	0
Pyrexia	9	1
Drooling	9	0
Decreased Appetite	7	2
Salivary Hypersecretion	6	1
Extrapyramidal Disorder	6	0
Lethargy	5	0

## Less Common Adverse Reactions in Pediatric Patients (6 to 17 years) with Schizophrenia, Bipolar Mania, or Autistic Disorder

Table 10 enumerates the pooled incidence, rounded to the nearest percent, of adverse reactions that occurred during acute therapy (up to 6 weeks in schizophrenia, up to 4 weeks in bipolar mania, and up to 8 weeks in autistic disorder), including only those reactions that occurred in 1% or more of pediatric patients treated with aripiprazole

(doses  $\geq 2$  mg/day) and for which the incidence in patients treated with aripiprazole was greater than the incidence in patients treated with placebo.

**Table 10: Adverse Reactions in Short-Term, Placebo-Controlled Trials of Pediatric Patients (6 to 17 years) Treated with Oral ABILIFY**

System Organ Class Preferred Term	Percentage of Patients Reporting Reaction <sup>a</sup>	
	Aripiprazole (n=611)	Placebo (n=298)
<b>Eye Disorders</b>		
Blurred Vision	3	0
<b>Gastrointestinal Disorders</b>		
Vomiting	9	7
Nausea	8	4
Diarrhea	5	3
Salivary Hypersecretion	4	1
Abdominal Pain Upper	3	2
Constipation	3	2
Dry Mouth	1	0
<b>General Disorders and Administration Site Conditions</b>		
Fatigue	10	2
Pyrexia	5	1
Irritability	1	0
Thirst	1	0
<b>Infections and Infestations</b>		
Nasopharyngitis	6	3
<b>Investigations</b>		
Weight Increased	2	1
<b>Metabolism and Nutrition Disorders</b>		
Increased Appetite	7	3
Decreased Appetite	4	2
<b>Musculoskeletal and Connective Tissue Disorders</b>		
Arthralgia	1	0
Musculoskeletal Stiffness	1	0
<b>Nervous System Disorders</b>		
Somnolence	16	4
Extrapyramidal Disorder	14	2
Headache	13	12
Sedation	8	1
Akathisia	6	1
Tremor	6	1
Drooling	4	0
Dizziness	3	1
Lethargy	2	0

**Table 10: Adverse Reactions in Short-Term, Placebo-Controlled Trials of Pediatric Patients (6 to 17 years) Treated with Oral ABILIFY**

System Organ Class Preferred Term	Percentage of Patients Reporting Reaction <sup>a</sup>	
	Aripiprazole (n=611)	Placebo (n=298)
Dystonia	1	0
Dyskinesia	1	0
Hypersomnia	1	0
<b>Reproductive System and Breast Disorders</b>		
Dysmenorrhoea*	2	1
<b>Respiratory, Thoracic, and Mediastinal Disorders</b>		
Rhinorrhoea	2	1
<b>Skin and Subcutaneous Disorders</b>		
Rash	2	1

<sup>a</sup> Adverse reactions reported by at least 1% of pediatric patients treated with oral aripiprazole, except adverse reactions which had an incidence equal to or less than placebo.  
\* Adjusted for gender.

### **Adult Patients Receiving ABILIFY as Adjunctive Treatment of Major Depressive Disorder**

The following findings are based on a pool of two placebo-controlled trials of patients with major depressive disorder in which aripiprazole was administered at doses of 2 mg to 20 mg as adjunctive treatment to continued antidepressant therapy.

#### *Adverse Reactions Associated with Discontinuation of Treatment*

The incidence of discontinuation due to adverse reactions was 6% for adjunctive aripiprazole-treated patients and 2% for adjunctive placebo-treated patients.

#### *Commonly Observed Adverse Reactions*

The commonly observed adverse reactions associated with the use of adjunctive aripiprazole in patients with major depressive disorder (incidence of 5% or greater and aripiprazole incidence at least twice that for placebo) were: akathisia, restlessness, insomnia, constipation, fatigue, and blurred vision.

#### *Less Common Adverse Reactions in Adult Patients with Major Depressive Disorder*

Table 11 enumerates the pooled incidence, rounded to the nearest percent, of adverse reactions that occurred during acute therapy (up to 6 weeks), including only those adverse

reactions that occurred in 2% or more of patients treated with adjunctive aripiprazole (doses  $\geq 2$  mg/day) and for which the incidence in patients treated with adjunctive aripiprazole was greater than the incidence in patients treated with adjunctive placebo in the combined dataset.

**Table 11: Adverse Reactions in Short-Term, Placebo-Controlled Adjunctive Trials in Patients with Major Depressive Disorder**

System Organ Class Preferred Term	Percentage of Patients Reporting Reaction <sup>a</sup>	
	Aripiprazole+ADT* (n=371)	Placebo+ADT* (n=366)
<b>Eye Disorders</b>		
Blurred Vision	6	1
<b>Gastrointestinal Disorders</b>		
Constipation	5	2
<b>General Disorders and Administration Site Conditions</b>		
Fatigue	8	4
Feeling Jittery	3	1
<b>Infections and Infestations</b>		
Upper Respiratory Tract Infection	6	4
<b>Investigations</b>		
Weight Increased	3	2
<b>Metabolism and Nutrition Disorders</b>		
Increased Appetite	3	2
<b>Musculoskeletal and Connective Tissue Disorders</b>		
Arthralgia	4	3
Myalgia	3	1
<b>Nervous System Disorders</b>		
Akathisia	25	4
Somnolence	6	4
Tremor	5	4
Sedation	4	2
Dizziness	4	2
Disturbance in Attention	3	1
Extrapyramidal Disorder	2	0
<b>Psychiatric Disorders</b>		
Restlessness	12	2
Insomnia	8	2

<sup>a</sup> Adverse reactions reported by at least 2% of patients treated with adjunctive aripiprazole, except adverse reactions which had an incidence equal to or less than placebo.

\* Antidepressant Therapy

## Patients with Agitation Associated with Schizophrenia or Bipolar Mania (Intramuscular Injection)

The following findings are based on a pool of three placebo-controlled trials of patients with agitation associated with schizophrenia or bipolar mania in which aripiprazole injection was administered at doses of 5.25 mg to 15 mg.

### *Adverse Reactions Associated with Discontinuation of Treatment*

Overall, in patients with agitation associated with schizophrenia or bipolar mania, there was little difference in the incidence of discontinuation due to adverse reactions between aripiprazole-treated (0.8%) and placebo-treated (0.5%) patients.

### *Commonly Observed Adverse Reactions*

There was one commonly observed adverse reaction (nausea) associated with the use of aripiprazole injection in patients with agitation associated with schizophrenia and bipolar mania (incidence of 5% or greater and aripiprazole incidence at least twice that for placebo).

### *Less Common Adverse Reactions in Patients with Agitation Associated with Schizophrenia or Bipolar Mania*

Table 12 enumerates the pooled incidence, rounded to the nearest percent, of adverse reactions that occurred during acute therapy (24-hour), including only those adverse reactions that occurred in 2% or more of patients treated with aripiprazole injection (doses  $\geq$ 5.25 mg/day) and for which the incidence in patients treated with aripiprazole injection was greater than the incidence in patients treated with placebo in the combined dataset.

**Table 12: Adverse Reactions in Short-Term, Placebo-Controlled Trials in Patients Treated with ABILIFY Injection**

System Organ Class Preferred Term	Percentage of Patients Reporting Reaction <sup>a</sup>	
	Aripiprazole (n=501)	Placebo (n=220)
<b>Cardiac Disorders</b>		
Tachycardia	2	<1
<b>Gastrointestinal Disorders</b>		
Nausea	9	3
Vomiting	3	1
<b>General Disorders and Administration Site Conditions</b>		
Fatigue	2	1
<b>Nervous System Disorders</b>		
Headache	12	7

**Table 12: Adverse Reactions in Short-Term, Placebo-Controlled Trials in Patients Treated with ABILIFY Injection**

System Organ Class Preferred Term	Percentage of Patients Reporting Reaction <sup>a</sup>	
	Aripiprazole (n=501)	Placebo (n=220)
Dizziness	8	5
Somnolence	7	4
Sedation	3	2
Akathisia	2	0

<sup>a</sup> Adverse reactions reported by at least 2% of patients treated with aripiprazole injection, except adverse reactions which had an incidence equal to or less than placebo.

## Dose-Related Adverse Reactions

### ***Schizophrenia***

Dose response relationships for the incidence of treatment-emergent adverse events were evaluated from four trials in adult patients with schizophrenia comparing various fixed doses (2 mg/day, 5 mg/day, 10 mg/day, 15 mg/day, 20 mg/day, and 30 mg/day) of oral aripiprazole to placebo. This analysis, stratified by study, indicated that the only adverse reaction to have a possible dose response relationship, and then most prominent only with 30 mg, was somnolence [including sedation]; (incidences were placebo, 7.1%; 10 mg, 8.5%; 15 mg, 8.7%; 20 mg, 7.5%; 30 mg, 12.6%).

In the study of pediatric patients (13 to 17 years of age) with schizophrenia, three common adverse reactions appeared to have a possible dose response relationship: extrapyramidal disorder (incidences were placebo, 5.0%; 10 mg, 13.0%; 30 mg, 21.6%); somnolence (incidences were placebo, 6.0%; 10 mg, 11.0%; 30 mg, 21.6%); and tremor (incidences were placebo, 2.0%; 10 mg, 2.0%; 30 mg, 11.8%).

### ***Bipolar Mania***

In the study of pediatric patients (10 to 17 years of age) with bipolar mania, four common adverse reactions had a possible dose response relationship at 4 weeks; extrapyramidal disorder (incidences were placebo, 3.1%; 10 mg, 12.2%; 30 mg, 27.3%); somnolence (incidences were placebo, 3.1%; 10 mg, 19.4%; 30 mg, 26.3%); akathisia (incidences were placebo, 2.1%; 10 mg, 8.2%; 30 mg, 11.1%); and salivary hypersecretion (incidences were placebo, 0%; 10 mg, 3.1%; 30 mg, 8.1%).

### ***Autistic Disorder***

In a study of pediatric patients (6 to 17 years of age) with autistic disorder, one common adverse reaction had a possible dose response relationship: fatigue (incidences were placebo, 0%; 5 mg, 3.8%; 10 mg, 22.0%; 15 mg, 18.5%).

### **Extrapyramidal Symptoms**

#### ***Schizophrenia***

In short-term, placebo-controlled trials in schizophrenia in adults, the incidence of reported EPS-related events, excluding events related to akathisia, for aripiprazole-treated patients was 13% vs. 12% for placebo; and the incidence of akathisia-related events for aripiprazole-treated patients was 8% vs. 4% for placebo. In the short-term, placebo-controlled trial of schizophrenia in pediatric (13 to 17 years) patients, the incidence of reported EPS-related events, excluding events related to akathisia, for aripiprazole-treated patients was 25% vs. 7% for placebo; and the incidence of akathisia-related events for aripiprazole-treated patients was 9% vs. 6% 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 adult 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 pediatric (13 to 17 years) schizophrenia trial, the objectively collected data did not show a difference between aripiprazole and placebo, with the exception of the Simpson Angus Rating Scale (aripiprazole, 0.24; placebo, -0.29).

Similarly, in a long-term (26-week), placebo-controlled trial of schizophrenia in adults, 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.

#### ***Bipolar Mania***

In the short-term, placebo-controlled trials in bipolar mania in adults, the incidence of reported EPS-related events, excluding events related to akathisia, for monotherapy aripiprazole-treated patients was 16% vs. 8% for placebo and the incidence of akathisia-related events for monotherapy aripiprazole-treated patients was 13% vs. 4% for placebo.

In the 6-week, placebo-controlled trial in bipolar mania for adjunctive therapy with lithium or valproate, the incidence of reported EPS-related events, excluding events related to akathisia for adjunctive aripiprazole-treated patients was 15% vs. 8% for adjunctive placebo and the incidence of akathisia-related events for adjunctive aripiprazole-treated patients was 19% vs. 5% for adjunctive placebo. In the short-term, placebo-controlled trial in bipolar mania in pediatric (10 to 17 years) patients, the incidence of reported EPS-related events, excluding events related to akathisia, for aripiprazole-treated patients was 26% vs. 5% for placebo and the incidence of akathisia-related events for aripiprazole-treated patients was 10% vs. 2% for placebo.

In the adult bipolar mania trials with monotherapy aripiprazole, the Simpson Angus Rating Scale and the Barnes Akathisia Scale showed a significant difference between aripiprazole and placebo (aripiprazole, 0.50; placebo, -0.01 and aripiprazole, 0.21; placebo, -0.05). Changes in the Assessments of Involuntary Movement Scales were similar for the aripiprazole and placebo groups. In the bipolar mania trials with aripiprazole as adjunctive therapy with either lithium or valproate, the Simpson Angus Rating Scale and the Barnes Akathisia Scale showed a significant difference between adjunctive aripiprazole and adjunctive placebo (aripiprazole, 0.73; placebo, 0.07 and aripiprazole, 0.30; placebo, 0.11). Changes in the Assessments of Involuntary Movement Scales were similar for adjunctive aripiprazole and adjunctive placebo. In the pediatric (10 to 17 years) short-term bipolar mania trial, the Simpson Angus Rating Scale showed a significant difference between aripiprazole and placebo (aripiprazole, 0.90; placebo, -0.05). Changes in the Barnes Akathisia Scale and the Assessments of Involuntary Movement Scales were similar for the aripiprazole and placebo groups.

### ***Major Depressive Disorder***

In the short-term, placebo-controlled trials in major depressive disorder, the incidence of reported EPS-related events, excluding events related to akathisia, for adjunctive aripiprazole-treated patients was 8% vs. 5% for adjunctive placebo-treated patients; and the incidence of akathisia-related events for adjunctive aripiprazole-treated patients was 25% vs. 4% for adjunctive placebo-treated patients.

In the major depressive disorder trials, the Simpson Angus Rating Scale and the Barnes Akathisia Scale showed a significant difference between adjunctive aripiprazole and adjunctive placebo (aripiprazole, 0.31; placebo, 0.03 and aripiprazole, 0.22; placebo, 0.02). Changes in the Assessments of Involuntary Movement Scales were similar for the adjunctive aripiprazole and adjunctive placebo groups.

### ***Autistic Disorder***

In the short-term, placebo-controlled trials in autistic disorder in pediatric patients (6 to 17 years), the incidence of reported EPS-related events, excluding events related to akathisia, for aripiprazole-treated patients was 18% vs. 2% for placebo and the incidence of akathisia-related events for aripiprazole-treated patients was 3% vs. 9% for placebo.

In the pediatric (6 to 17 years) short-term autistic disorder trials, the Simpson Angus Rating Scale showed a significant difference between aripiprazole and placebo (aripiprazole, 0.1; placebo, -0.4). Changes in the Barnes Akathisia Scale and the Assessments of Involuntary Movement Scales were similar for the aripiprazole and placebo groups.

### ***Agitation Associated with Schizophrenia or Bipolar Mania***

In the placebo-controlled trials in patients with agitation associated with schizophrenia or bipolar mania, the incidence of reported EPS-related events excluding events related to akathisia for aripiprazole-treated patients was 2% vs. 2% for placebo and the incidence of akathisia-related events for aripiprazole-treated patients was 2% vs. 0% for placebo. Objectively collected data on the Simpson Angus Rating Scale (for EPS) and the Barnes Akathisia Scale (for akathisia) for all treatment groups did not show a difference between aripiprazole and placebo.

### ***Dystonia***

*Class Effect:* Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

### ***Laboratory Test Abnormalities***

A between group comparison for 3-week to 6-week, placebo-controlled trials in adults or 4-week to 8-week, placebo-controlled trials in pediatric patients (6 to 17 years) 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 adult or pediatric patients.

In the 6-week trials of aripiprazole as adjunctive therapy for major depressive disorder, there were no clinically important differences between the adjunctive aripiprazole-treated and adjunctive placebo-treated patients in the median change from baseline in prolactin, fasting glucose, HDL, LDL, or total cholesterol measurements. The median % change from baseline in triglycerides was 5% for adjunctive aripiprazole-treated patients vs. 0% for adjunctive placebo-treated patients.

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, or total cholesterol measurements.

### **Weight Gain**

In 4-week to 6-week trials in adults with 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 a 6-week trial in pediatric patients (13 to 17 years) with schizophrenia, there was a slight difference in mean weight gain between aripiprazole and placebo patients (+0.13 kg vs. -0.83 kg, respectively) and also a difference in the proportion of patients meeting a weight gain criterion of  $\geq 7\%$  of body weight [aripiprazole (5%) compared to placebo (1%)].

In 3-week trials in adults with mania with monotherapy aripiprazole, the mean weight gain for aripiprazole and placebo patients was 0.1 kg vs. 0.0 kg, respectively. The proportion of patients meeting a weight gain criterion of  $\geq 7\%$  of body weight was aripiprazole (2%) compared to placebo (3%). In the 6-week trial in mania with aripiprazole as adjunctive therapy with either lithium or valproate, the mean weight gain for aripiprazole and placebo patients was 0.6 kg vs. 0.2 kg, respectively. The proportion of patients meeting a weight gain criterion of  $\geq 7\%$  of body weight with adjunctive aripiprazole was 3% compared to adjunctive placebo 4%.

In the trials adding aripiprazole to antidepressants, patients first received 8 weeks of antidepressant treatment followed by 6 weeks of adjunctive aripiprazole or placebo in

addition to their ongoing antidepressant treatment. The mean weight gain with adjunctive aripiprazole was 1.7 kg vs. 0.4 kg with adjunctive placebo. The proportion of patients meeting a weight gain criterion of  $\geq 7\%$  of body weight was 5% with adjunctive aripiprazole compared to 1% with adjunctive placebo.

In the two short term, placebo-controlled trials in patients (6 to 17 years) with autistic disorder, the mean increase in body weight in the aripiprazole group was 1.6 kg vs. 0.4 kg in the placebo group. The proportion of patients meeting a weight gain criterion of  $\geq 7\%$  of body weight was 26% in aripiprazole group compared to 7% in placebo group.

Table 13 provides the weight change results from a long-term (26-week), placebo-controlled study of aripiprazole in adults with schizophrenia, 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. Although there was no mean weight increase, the aripiprazole group tended to show more patients with a  $\geq 7\%$  weight gain.

**Table 13: Weight Change Results Categorized by BMI at Baseline: Placebo-Controlled Study in Schizophrenia, Safety Sample**

	BMI <23		BMI 23-27		BMI >27	
	Placebo (n=54)	Aripiprazole (n=59)	Placebo (n=48)	Aripiprazole (n=39)	Placebo (n=49)	Aripiprazole (n=53)
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 14 provides the weight change results from a long-term (52-week) study of aripiprazole in adults with schizophrenia, 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 14: Weight Change Results Categorized by BMI at Baseline: Active-Controlled Study in Schizophrenia, Safety Sample**

	BMI <23 (n=314)	BMI 23-27 (n=265)	BMI >27 (n=260)
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 a pooled analysis of placebo-controlled trials in patients with schizophrenia, bipolar mania, or major depressive disorder revealed no significant differences between oral aripiprazole and placebo in the proportion of patients experiencing potentially important changes in ECG parameters. Aripiprazole was associated with a median increase in heart rate of 2 beats per minute compared to no increase among placebo patients.

In the pooled, placebo-controlled trials in patients with agitation associated with schizophrenia or bipolar mania, there were no significant differences between aripiprazole injection and placebo in the proportion of patients experiencing potentially important changes in ECG parameters, as measured by standard 12-lead ECGs.

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

### ***Adverse Reactions in Long-Term, Double-Blind, Placebo-Controlled Trials***

The adverse reactions reported in a 26-week, double-blind trial comparing oral ABILIFY and placebo in patients with schizophrenia were generally consistent with those reported in the short-term, placebo-controlled trials, except for a higher incidence of tremor [8% (12/153) for ABILIFY vs. 2% (3/153) for placebo]. In this study, the majority of the cases of tremor were of mild intensity (8/12 mild and 4/12 moderate), occurred early in therapy (9/12  $\leq$ 49 days), and were of limited duration (7/12  $\leq$ 10 days). Tremor infrequently led to discontinuation (<1%) of ABILIFY. In addition, in a long-term (52-week), active-controlled study, the incidence of tremor was 5% (40/859) for ABILIFY. A similar profile was observed in a long-term study in bipolar disorder.

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

Following is a list of MedDRA terms that reflect adverse reactions as defined in *ADVERSE REACTIONS (6.1)* reported by patients treated with oral aripiprazole at multiple doses  $\geq$ 2 mg/day during any phase of a trial within the database of 13,543 adult patients. All events assessed as possible adverse drug reactions have been included with the exception of more commonly occurring events. In addition, medically/clinically meaningful adverse reactions, particularly those that are likely to be useful to the prescriber or that have pharmacologic plausibility, have been included. Events already listed in other parts of *ADVERSE REACTIONS (6)*, or those considered in *WARNINGS*

*AND PRECAUTIONS (5) or OVERDOSAGE (10)* have been excluded. Although the reactions reported occurred during treatment with aripiprazole, they were not necessarily caused by it.

Events are further categorized by MedDRA system organ class and listed in order of decreasing frequency according to the following definitions: 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); those occurring in 1/100 to 1/1000 patients; and those occurring in fewer than 1/1000 patients.

### **Adults - Oral Administration**

#### *Blood and Lymphatic System Disorders:*

$\geq 1/1000$  patients and  $< 1/100$  patients - leukopenia, neutropenia, thrombocytopenia

#### *Cardiac Disorders:*

$\geq 1/1000$  patients and  $< 1/100$  patients - bradycardia, palpitations, cardiopulmonary failure, myocardial infarction, cardio-respiratory arrest, atrioventricular block, extrasystoles, sinus tachycardia, atrial fibrillation, angina pectoris, myocardial ischemia;  $< 1/1000$  patients - atrial flutter, supraventricular tachycardia, ventricular tachycardia

#### *Eye Disorders:*

$\geq 1/1000$  patients and  $< 1/100$  patients - photophobia, diplopia, eyelid edema, photopsia

#### *Gastrointestinal Disorders:*

$\geq 1/1000$  patients and  $< 1/100$  patients - gastroesophageal reflux disease, swollen tongue, esophagitis;  $< 1/1000$  patients - pancreatitis

#### *General Disorders and Administration Site Conditions:*

$\geq 1/100$  patients - asthenia, peripheral edema, chest pain;  $\geq 1/1000$  patients and  $< 1/100$  patients - face edema, angioedema;  $< 1/1000$  patients - hypothermia

#### *Hepatobiliary Disorders:*

$< 1/1000$  patients - hepatitis, jaundice

#### *Immune System Disorders:*

$\geq 1/1000$  patients and  $< 1/100$  patients - hypersensitivity

#### *Injury, Poisoning, and Procedural Complications:*

$\geq 1/100$  patients - fall;  $\geq 1/1000$  patients and  $< 1/100$  patients - self mutilation;  $< 1/1000$  patients - heat stroke

*Investigations:*

$\geq 1/100$  patients - weight decreased, creatine phosphokinase increased;  $\geq 1/1000$  patients and  $< 1/100$  patients - hepatic enzyme increased, blood glucose increased, blood prolactin increased, blood urea increased, electrocardiogram QT prolonged, blood creatinine increased, blood bilirubin increased;  $< 1/1000$  patients - blood lactate dehydrogenase increased, glycosylated hemoglobin increased, gamma-glutamyl transferase increased

*Metabolism and Nutrition Disorders:*

$\geq 1/1000$  patients and  $< 1/100$  patients - hyperlipidemia, anorexia, diabetes mellitus (including blood insulin increased, carbohydrate tolerance decreased, diabetes mellitus non-insulin-dependent, glucose tolerance impaired, glycosuria, glucose urine, glucose urine present), hyperglycemia, hypokalemia, hyponatremia, hypoglycemia, polydipsia;  $< 1/1000$  patients - diabetic ketoacidosis

*Musculoskeletal and Connective Tissue Disorders:*

$\geq 1/1000$  patients and  $< 1/100$  patients - muscle rigidity, muscular weakness, muscle tightness, mobility decreased;  $< 1/1000$  patients - rhabdomyolysis

*Nervous System Disorders:*

$\geq 1/100$  patients - coordination abnormal;  $\geq 1/1000$  patients and  $< 1/100$  patients - speech disorder, parkinsonism, memory impairment, cogwheel rigidity, cerebrovascular accident, hypokinesia, tardive dyskinesia, hypotonia, myoclonus, hypertonia, akinesia, bradykinesia;  $< 1/1000$  patients - Grand Mal convulsion, choreoathetosis

*Psychiatric Disorders:*

$\geq 1/100$  patients - suicidal ideation;  $\geq 1/1000$  patients and  $< 1/100$  patients - aggression, loss of libido, suicide attempt, hostility, libido increased, anger, anorgasmia, delirium, intentional self injury, completed suicide, tic, homicidal ideation;  $< 1/1000$  patients - catatonia, sleep walking

*Renal and Urinary Disorders:*

$\geq 1/1000$  patients and  $< 1/100$  patients - urinary retention, polyuria, nocturia

*Reproductive System and Breast Disorders:*

$\geq 1/1000$  patients and  $< 1/100$  patients - menstruation irregular, erectile dysfunction, amenorrhea, breast pain;  $< 1/1000$  patients - gynaecomastia, priapism

*Respiratory, Thoracic, and Mediastinal Disorders:*

$\geq 1/100$  patients - nasal congestion, dyspnea, pneumonia aspiration

*Skin and Subcutaneous Tissue Disorders:*

$\geq 1/100$  patients - rash (including erythematous, exfoliative, generalized, macular, maculopapular, papular rash; acneiform, allergic, contact, exfoliative, seborrheic dermatitis, neurodermatitis, and drug eruption), hyperhidrosis;  $\geq 1/1000$  patients and  $< 1/100$  patients - pruritus, photosensitivity reaction, alopecia, urticaria

*Vascular Disorders:*

$\geq 1/100$  patients - hypertension;  $\geq 1/1000$  patients and  $< 1/100$  patients - hypotension

**Pediatric Patients - Oral Administration**

Most adverse events observed in the pooled database of 920 pediatric patients aged 6 to 17 years were also observed in the adult population. Additional adverse reactions observed in the pediatric population are listed below.

*Gastrointestinal Disorders:*

$\geq 1/1000$  patients and  $< 1/100$  patients - tongue dry, tongue spasm

*Investigations:*

$\geq 1/100$  patients - blood insulin increased

*Nervous System Disorders:*

$\geq 1/1000$  patients and  $< 1/100$  patients - sleep talking

*Skin and Subcutaneous Tissue Disorders:*

$\geq 1/1000$  patients and  $< 1/100$  patients - hirsutism

**Adults - Intramuscular Injection**

Most adverse reactions observed in the pooled database of 749 adult patients treated with aripiprazole injection, were also observed in the adult population treated with oral aripiprazole. Additional adverse reactions observed in the aripiprazole injection population are listed below.

*General Disorders and Administration Site Conditions:*

$\geq 1/100$  patients - injection site reaction;  $\geq 1/1000$  patients and  $< 1/100$  patients - venipuncture site bruise

### **6.3 Postmarketing Experience**

The following adverse reactions have been identified during postapproval use of ABILIFY. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to establish a causal relationship to drug exposure: rare occurrences of allergic reaction (anaphylactic reaction, angioedema, laryngospasm, pruritus/urticaria, or oropharyngeal spasm), and blood glucose fluctuation.

## 7 DRUG INTERACTIONS

Given the primary CNS effects of aripiprazole, caution should be used when ABILIFY is taken in combination with other centrally-acting drugs or alcohol.

Due to its alpha adrenergic antagonism, aripiprazole has the potential to enhance the effect of certain antihypertensive agents.

### 7.1 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 and Other CYP3A4 Inhibitors**

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 ketoconazole is given concomitantly with aripiprazole, the 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; moderate inhibitors (erythromycin, grapefruit juice) have not been studied. When the CYP3A4 inhibitor is withdrawn from the combination therapy, the aripiprazole dose should be increased.

#### **Quinidine and Other CYP2D6 Inhibitors**

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 quinidine is given

concomitantly with aripiprazole. Other significant inhibitors of CYP2D6, such as fluoxetine or paroxetine, would be expected to have similar effects and should lead to similar dose reductions. When the CYP2D6 inhibitor is withdrawn from the combination therapy, the aripiprazole dose should be increased. When adjunctive ABILIFY is administered to patients with major depressive disorder, ABILIFY should be administered without dosage adjustment as specified in *DOSAGE AND ADMINISTRATION* (2.3).

### **Carbamazepine and Other CYP3A4 Inducers**

Coadministration of carbamazepine (200 mg twice daily), a potent CYP3A4 inducer, with aripiprazole (30 mg/day) resulted in an approximate 70% decrease in C<sub>max</sub> and AUC values of both aripiprazole and its active metabolite, dehydro-aripiprazole. When carbamazepine is added to aripiprazole therapy, aripiprazole dose should be doubled. Additional dose increases should be based on clinical evaluation. When carbamazepine is withdrawn from the combination therapy, the aripiprazole dose should be reduced.

## **7.2 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 mg/day 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*.

No effect of aripiprazole was seen on the pharmacokinetics of lithium or valproate.

### **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.

## **7.3 Drugs Having No Clinically Important Interactions with ABILIFY**

### **Famotidine**

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

### **Valproate**

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

When aripiprazole (30 mg/day) and valproate (1000 mg/day) were coadministered, at steady-state there were no clinically significant changes in the C<sub>max</sub> or AUC of valproate. No dosage adjustment of valproate is required when administered concomitantly with aripiprazole.

### **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 mg/day-1800 mg/day) for 21 days with aripiprazole (30 mg/day) did not result in clinically significant changes in the pharmacokinetics of aripiprazole or its active metabolite, dehydro-aripiprazole (C<sub>max</sub> and AUC increased by less than 20%). No dosage adjustment of aripiprazole is required when administered concomitantly with lithium.

Coadministration of aripiprazole (30 mg/day) with lithium (900 mg/day) did not result in clinically significant changes in the pharmacokinetics of lithium. No dosage adjustment of lithium is required when administered concomitantly with aripiprazole.

## **Lamotrigine**

Coadministration of 10 mg/day to 30 mg/day oral doses of aripiprazole for 14 days to patients with bipolar I disorder had no effect on the steady-state pharmacokinetics of 100 mg/day to 400 mg/day lamotrigine, a UDP-glucuronosyltransferase 1A4 substrate. No dosage adjustment of lamotrigine is required when aripiprazole is added to lamotrigine.

## **Dextromethorphan**

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

## **Warfarin**

Aripiprazole 10 mg/day for 14 days had no effect on the pharmacokinetics of R-warfarin 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/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.

## **Lorazepam**

Coadministration of lorazepam injection (2 mg) and aripiprazole injection (15 mg) to healthy subjects (n=40: 35 males and 5 females; ages 19-45 years old) did not result in clinically important changes in the pharmacokinetics of either drug. No dosage adjustment of aripiprazole is required when administered concomitantly with lorazepam. However, the intensity of sedation was greater with the combination as compared to that observed with aripiprazole alone and the orthostatic hypotension observed was greater with the combination as compared to that observed with lorazepam alone [*see WARNINGS AND PRECAUTIONS (5.6)*].

## **Escitalopram**

Coadministration of 10 mg/day oral doses of aripiprazole for 14 days to healthy subjects had no effect on the steady-state pharmacokinetics of 10 mg/day escitalopram, a substrate of CYP2C19 and CYP3A4. No dosage adjustment of escitalopram is required when aripiprazole is added to escitalopram.

## **Venlafaxine**

Coadministration of 10 mg/day to 20 mg/day oral doses of aripiprazole for 14 days to healthy subjects had no effect on the steady-state pharmacokinetics of venlafaxine and O-desmethylvenlafaxine following 75 mg/day venlafaxine XR, a CYP2D6 substrate. No dosage adjustment of venlafaxine is required when aripiprazole is added to venlafaxine.

## **Fluoxetine, Paroxetine, and Sertraline**

A population pharmacokinetic analysis in patients with major depressive disorder showed no substantial change in plasma concentrations of fluoxetine (20 mg/day or 40 mg/day), paroxetine CR (37.5 mg/day or 50 mg/day), or sertraline (100 mg/day or 150 mg/day) dosed to steady-state. The steady-state plasma concentrations of fluoxetine and norfluoxetine increased by about 18% and 36%, respectively, and concentrations of paroxetine decreased by about 27%. The steady-state plasma concentrations of sertraline and desmethylsertraline were not substantially changed when these antidepressant therapies were coadministered with aripiprazole. Aripiprazole dosing was 2 mg/day to 15 mg/day (when given with fluoxetine or paroxetine) or 2 mg/day to 20 mg/day (when given with sertraline).

## **8 USE IN SPECIFIC 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 (2.5)*].

### **8.1 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 mg/kg/day, 10 mg/kg/day, and 30 mg/kg/day (1 times, 3 times, and 10 times the maximum recommended human dose

[MRHD] on a  $\text{mg}/\text{m}^2$  basis) of aripiprazole during the period of organogenesis. Gestation was slightly prolonged at 30 mg/kg. Treatment caused a slight delay in fetal development, as evidenced by decreased fetal weight (30 mg/kg), undescended testes (30 mg/kg), and delayed skeletal ossification (10 mg/kg and 30 mg/kg). There were no adverse effects on embryofetal or pup survival. Delivered offspring had decreased body weights (10 mg/kg 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 mg/kg and 30 mg/kg and impaired reproductive performance (decreased fertility rate, corpora lutea, implants, 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.

In pregnant rats receiving aripiprazole injection intravenously (3 mg/kg/day, 9 mg/kg/day, and 27 mg/kg/day) during the period of organogenesis, decreased fetal weight and delayed skeletal ossification were seen at the highest dose, which also caused some maternal toxicity.

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

In pregnant rabbits receiving aripiprazole injection intravenously (3 mg/kg/day, 10 mg/kg/day, and 30 mg/kg/day) during the period of organogenesis, the highest dose, which caused pronounced maternal toxicity, resulted in decreased fetal weight, increased fetal abnormalities (primarily skeletal), and decreased fetal skeletal ossification. The fetal no-effect dose was 10 mg/kg, which produced 5 times the human exposure at the MRHD based on AUC and is 6 times the MRHD based on  $\text{mg}/\text{m}^2$ .

In a study in which rats were treated with oral doses of 3 mg/kg/day, 10 mg/kg/day, and 30 mg/kg/day (1 times, 3 times, and 10 times the MRHD on a  $\text{mg}/\text{m}^2$  basis) of

aripiprazole perinatally and postnatally (from day 17 of gestation through day 21 postpartum), slight maternal toxicity and slightly prolonged gestation were seen at 30 mg/kg. An increase in stillbirths and decreases in pup weight (persisting into adulthood) and survival were seen at this dose.

In rats receiving aripiprazole injection intravenously (3 mg/kg/day, 8 mg/kg/day, and 20 mg/kg/day) from day 6 of gestation through day 20 postpartum, an increase in stillbirths was seen at 8 mg/kg and 20 mg/kg, and decreases in early postnatal pup weights and survival were seen at 20 mg/kg. These doses produced some maternal toxicity. There were no effects on postnatal behavioral and reproductive development.

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.

## **8.2 Labor and Delivery**

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

## **8.3 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.

## **8.4 Pediatric Use**

Safety and effectiveness in pediatric patients with major depressive disorder or agitation associated with schizophrenia or bipolar mania have not been established.

Safety and effectiveness in pediatric patients with schizophrenia were established in a 6-week, placebo-controlled clinical trial in 202 pediatric patients aged 13 to 17 years [*see INDICATIONS AND USAGE (1.1), DOSAGE AND ADMINISTRATION (2.1), ADVERSE REACTIONS (6.2), and CLINICAL STUDIES (14.1)*]. Although maintenance efficacy in pediatric patients has not been systematically evaluated, maintenance efficacy can be extrapolated from adult data along with comparisons of aripiprazole pharmacokinetic parameters in adult and pediatric patients.

Safety and effectiveness in pediatric patients with bipolar mania were established in a 4-week, placebo-controlled clinical trial in 197 pediatric patients aged 10 to 17 years [see *INDICATIONS AND USAGE (1.2)*, *DOSAGE AND ADMINISTRATION (2.2)*, *ADVERSE REACTIONS (6.2)*, and *CLINICAL STUDIES (14.2)*]. Although maintenance efficacy in pediatric patients has not been systematically evaluated, maintenance efficacy can be extrapolated from adult data along with comparisons of aripiprazole pharmacokinetic parameters in adult and pediatric patients.

The efficacy of adjunctive ABILIFY with concomitant lithium or valproate in the treatment of manic or mixed episodes in pediatric patients has not been systematically evaluated. However, such efficacy and lack of pharmacokinetic interaction between aripiprazole and lithium or valproate can be extrapolated from adult data, along with comparisons of aripiprazole pharmacokinetic parameters in adult and pediatric patients.

Safety and effectiveness in pediatric patients demonstrating irritability associated with autistic disorder were established in two 8-week, placebo-controlled clinical trials in 212 pediatric patients aged 6 to 17 years [see *INDICATIONS AND USAGE (1.4)*, *DOSAGE AND ADMINISTRATION (2.4)*, *ADVERSE REACTIONS (6.2)*, and *CLINICAL STUDIES (14.4)*]. Maintenance efficacy in pediatric patients has not been systematically evaluated.

The pharmacokinetics of aripiprazole and dehydro-aripiprazole in pediatric patients 10 to 17 years of age were similar to those in adults after correcting for the differences in body weights.

## **8.5 Geriatric Use**

In formal single-dose pharmacokinetic studies (with aripiprazole given in a single dose of 15 mg), aripiprazole clearance was 20% lower in elderly ( $\geq 65$  years) subjects compared to younger adult subjects (18 to 64 years). There was no detectable age effect, however, in the population pharmacokinetic analysis in schizophrenia patients. Also, the pharmacokinetics of aripiprazole after multiple doses in elderly patients appeared similar to that observed in young, healthy subjects. No dosage adjustment is recommended for elderly patients [see also *BOXED WARNING* and *WARNINGS AND PRECAUTIONS (5.1)*].

Of the 13,543 patients treated with oral aripiprazole in clinical trials, 1073 (8%) were  $\geq 65$  years old and 799 (6%) were  $\geq 75$  years old. The majority (81%) of the 1073 patients were diagnosed with Dementia of the Alzheimer's type.

Placebo-controlled studies of oral aripiprazole in schizophrenia, bipolar mania, or major depressive disorder did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Of the 749 patients treated with aripiprazole injection in clinical trials, 99 (13%) were  $\geq 65$  years old and 78 (10%) were  $\geq 75$  years old. Placebo-controlled studies of aripiprazole injection in patients with agitation associated with schizophrenia or bipolar mania did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

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 also BOXED WARNING and WARNINGS AND PRECAUTIONS (5.1)*]. 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.

## **8.6 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.

## **8.7 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.

## **8.8 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.

## **8.9 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.

## **8.10 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.

# **9 DRUG ABUSE AND DEPENDENCE**

## **9.1 Controlled Substance**

ABILIFY is not a controlled substance.

## **9.2 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).

## 10 OVERDOSAGE

MedDRA terminology has been used to classify the adverse reactions.

### 10.1 Human Experience

A total of 76 cases of deliberate or accidental overdose with oral aripiprazole have been reported worldwide. These include overdoses with oral aripiprazole alone and in combination with other substances. No fatality was reported from these cases. Of the 44 cases with known outcome, 33 cases recovered without sequelae and one case recovered with sequelae (mydriasis and feeling abnormal). The largest known case of acute ingestion with a known outcome involved 1080 mg of oral 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 oral aripiprazole ingestions up to 195 mg with no fatalities.

Common adverse reactions (reported in at least 5% of all overdose cases) reported with oral 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.

### 10.2 Management of Overdosage

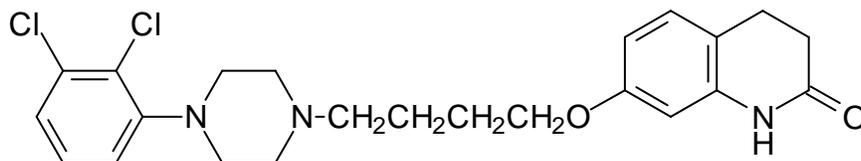
No specific information is available on the treatment of overdose with aripiprazole. An electrocardiogram should be obtained in case of overdose and if QT interval prolongation is present, cardiac monitoring should be instituted. Otherwise, management of overdose should concentrate on supportive therapy, 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<sub>max</sub> of aripiprazole by 50%.

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

## 11 DESCRIPTION

Aripiprazole is a psychotropic drug that is available as ABILIFY<sup>®</sup> (aripiprazole) Tablets, ABILIFY DISCMELT<sup>®</sup> (aripiprazole) Orally Disintegrating Tablets, ABILIFY<sup>®</sup> (aripiprazole) Oral Solution, and ABILIFY<sup>®</sup> (aripiprazole) Injection, a solution for intramuscular injection. Aripiprazole is 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydrocarbostyryl. The empirical formula is C<sub>23</sub>H<sub>27</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>2</sub> and its molecular weight is 448.39. The chemical structure is:



ABILIFY Tablets are available in 2 mg, 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 DISCMELT Orally Disintegrating Tablets are available in 10 mg and 15 mg strengths. Inactive ingredients include acesulfame potassium, aspartame, calcium silicate, croscarmellose sodium, crospovidone, crème de vanilla (natural and artificial flavors), magnesium stearate, microcrystalline cellulose, silicon dioxide, tartaric acid, and xylitol. Colorants include ferric oxide (yellow or red) and FD&C Blue No. 2 Aluminum Lake.

ABILIFY Oral Solution is a clear, colorless to light yellow solution available in a concentration of 1 mg/mL. The inactive ingredients for this solution include disodium edetate, 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.

ABILIFY Injection is available in single-dose vials as a ready-to-use, 9.75 mg/1.3 mL (7.5 mg/mL) clear, colorless, sterile, aqueous solution for intramuscular use only. Inactive ingredients for this solution include 150 mg/mL of sulfobutylether  $\beta$ -cyclodextrin (SBECD), tartaric acid, sodium hydroxide, and water for injection.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

The mechanism of action of aripiprazole, as with other drugs having efficacy in schizophrenia, bipolar disorder, major depressive disorder, irritability associated with autistic disorder, and agitation associated with schizophrenia or bipolar disorder, is unknown. However, it has been proposed that the efficacy of aripiprazole is mediated through a combination of partial agonist activity at  $D_2$  and  $5-HT_{1A}$  receptors and antagonist activity at  $5-HT_{2A}$  receptors. Actions at receptors other than  $D_2$ ,  $5-HT_{1A}$ , and  $5-HT_{2A}$  may explain some of the other clinical effects of aripiprazole (eg, the orthostatic hypotension observed with aripiprazole may be explained by its antagonist activity at adrenergic  $\alpha_1$  receptors).

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

### 12.3 Pharmacokinetics

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

aripiprazole is mainly through hepatic metabolism involving two P450 isozymes, CYP2D6 and CYP3A4.

Pharmacokinetic studies showed that ABILIFY DISCMELT Orally Disintegrating Tablets are bioequivalent to ABILIFY Tablets.

## **ORAL ADMINISTRATION**

### **Absorption**

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

*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<sub>max</sub> and AUC values were 122% and 114%, respectively [*see DOSAGE AND ADMINISTRATION (2.6)*]. The single-dose pharmacokinetics of aripiprazole were linear and dose-proportional between the doses of 5 mg 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 mg/day to 30 mg/day aripiprazole for 14 days, there was dose-dependent D<sub>2</sub> receptor occupancy indicating brain penetration of aripiprazole in humans.

### **Metabolism and Elimination**

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

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, such as quinidine or fluoxetine in EMs, approximately doubles aripiprazole plasma exposure, and dose adjustment is needed [*see DRUG INTERACTIONS (7.1)*]. The mean elimination half-lives are about 75 hours and 146 hours for aripiprazole in EMs and PMs, respectively. Aripiprazole does not inhibit or induce the CYP2D6 pathway.

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

## **INTRAMUSCULAR ADMINISTRATION**

In two pharmacokinetic studies of aripiprazole injection administered intramuscularly to healthy subjects, the median times to the peak plasma concentrations were at 1 hour and 3 hours. A 5 mg intramuscular injection of aripiprazole had an absolute bioavailability of 100%. The geometric mean maximum concentration achieved after an intramuscular dose was on average 19% higher than the C<sub>max</sub> of the oral tablet. While the systemic exposure over 24 hours was generally similar between aripiprazole injection given intramuscularly and after oral tablet administration, the aripiprazole AUC in the first 2 hours after an intramuscular injection was 90% greater than the AUC after the same dose as a tablet. In stable patients with schizophrenia or Schizoaffective Disorder, the pharmacokinetics of aripiprazole after intramuscular administration were linear over a dose range of 1 mg to 45 mg. Although the metabolism of aripiprazole injection was not systematically evaluated, the intramuscular route of administration would not be expected to alter the metabolic pathways.

## 13 NONCLINICAL TOXICOLOGY

### 13.1 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 mg/kg/day, 3 mg/kg/day, 10 mg/kg/day, and 30 mg/kg/day to ICR mice and 1 mg/kg/day, 3 mg/kg/day, and 10 mg/kg/day to F344 rats (0.2 times to 5 times and 0.3 times to 3 times the maximum recommended human dose [MRHD] based on  $\text{mg}/\text{m}^2$ , respectively). In addition, SD rats were dosed orally for 2 years at 10 mg/kg/day, 20 mg/kg/day, 40 mg/kg/day, and 60 mg/kg/day (3 times to 19 times the MRHD based on  $\text{mg}/\text{m}^2$ ). 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 mg/kg/day to 30 mg/kg/day (0.1 times to 0.9 times human exposure at MRHD based on AUC and 0.5 times to 5 times the MRHD based on  $\text{mg}/\text{m}^2$ ). 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  $\text{mg}/\text{m}^2$ ); 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  $\text{mg}/\text{m}^2$ ).

Proliferative changes in the pituitary and mammary gland of rodents have been observed following chronic administration of other antipsychotic agents and are considered prolactin-mediated. Serum prolactin was not measured in the aripiprazole carcinogenicity studies. However, increases in serum prolactin levels were observed in female mice in a 13-week dietary study at the doses associated with mammary gland and pituitary tumors. Serum prolactin was not increased in female rats in 4-week 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 due to a mechanism not considered relevant to humans.

### **Impairment of Fertility**

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

Male rats were treated with oral doses of 20 mg/kg/day, 40 mg/kg/day, and 60 mg/kg/day (6 times, 13 times, and 19 times the MRHD on a mg/m<sup>2</sup> basis) of aripiprazole from 9 weeks prior to mating through mating. Disturbances in spermatogenesis were seen at 60 mg/kg and prostate atrophy was seen at 40 mg/kg and 60 mg/kg, but no impairment of fertility was seen.

## **13.2 Animal Toxicology and/or Pharmacology**

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 mg/kg and 60 mg/kg. The 40 mg/kg and 60 mg/kg doses are 13 times and 19 times the maximum recommended human dose (MRHD) based on mg/m<sup>2</sup> and 7 times 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.

## 14 CLINICAL STUDIES

### 14.1 Schizophrenia

#### Adults

The efficacy of ABILIFY in the treatment of schizophrenia was evaluated in five short-term (4-week and 6-week), placebo-controlled trials of acutely relapsed inpatients who predominantly met DSM-III/IV criteria for schizophrenia. Four of the five 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 four 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 mg/day or 30 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 mg/day or 30 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 mg/day, 15 mg/day, 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 6-week trial (n=367) comparing three fixed doses of ABILIFY (2 mg/day, 5 mg/day, or 10 mg/day) to placebo, the 10 mg dose of ABILIFY was superior to placebo in the PANSS total score, the primary outcome measure of the study. The 2 mg and 5 mg doses did not demonstrate superiority to placebo on the primary outcome measure.

In a fifth study, a 4-week trial (n=103) comparing ABILIFY in a range of 5 mg/day to 30 mg/day to placebo, ABILIFY was only significantly different compared to placebo in a responder analysis based on the CGI-severity score, a primary outcome for that trial.

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

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/day or placebo for up to 26 weeks of observation for relapse. Relapse during the double-blind phase was defined as CGI-Improvement score of  $\geq 5$  (minimally worse), scores  $\geq 5$  (moderately severe) on the hostility or uncooperativeness items of the PANSS, or  $\geq 20\%$  increase in the PANSS total score. Patients receiving ABILIFY 15 mg/day experienced a significantly longer time to relapse over the subsequent 26 weeks compared to those receiving placebo.

### **Pediatric Patients**

The efficacy of ABILIFY (aripiprazole) in the treatment of schizophrenia in pediatric patients (13 to 17 years of age) was evaluated in one 6-week, placebo-controlled trial of outpatients who met DSM-IV criteria for schizophrenia and had a PANSS score  $\geq 70$  at

baseline. In this trial (n=302) comparing two fixed doses of ABILIFY (10 mg/day or 30 mg/day) to placebo, ABILIFY was titrated starting from 2 mg/day to the target dose in 5 days in the 10 mg/day treatment arm and in 11 days in the 30 mg/day treatment arm. Both doses of ABILIFY were superior to placebo in the PANSS total score, the primary outcome measure of the study. The 30 mg/day dosage was not shown to be more efficacious than the 10 mg/day dose. Although maintenance efficacy in pediatric patients has not been systematically evaluated, maintenance efficacy can be extrapolated from adult data along with comparisons of aripiprazole pharmacokinetic parameters in adult and pediatric patients.

## **14.2 Bipolar Disorder**

### **Monotherapy**

#### ***Adults***

The efficacy of ABILIFY in the acute treatment of manic episodes was established in four 3-week, placebo-controlled trials in hospitalized patients who met the DSM-IV criteria for bipolar I disorder with manic or mixed episodes. These studies included patients with or without psychotic features and two of the studies also included patients 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 four positive, 3-week, placebo-controlled trials (n=268; n=248; n=480; n=485) which evaluated ABILIFY in a range of 15 mg to 30 mg, once daily (with a starting dose of 15 mg/day in two studies and 30 mg/day in two studies), ABILIFY was superior to placebo in the reduction of Y-MRS total score and CGI-BP Severity of Illness score (mania). In the two studies with a starting dose of 15 mg/day, 48% and 44% of patients were on 15 mg/day at endpoint. In the two studies with a starting dose of 30 mg/day, 86% and 85% of patients were on 30 mg/day at endpoint.

A trial was conducted in patients meeting DSM-IV criteria for bipolar I disorder with a recent manic or mixed episode who had been stabilized on open-label ABILIFY and who had maintained a clinical response for at least 6 weeks. The first phase of this trial was an open-label stabilization period in which inpatients and outpatients were clinically stabilized and then maintained on open-label ABILIFY (15 mg/day or 30 mg/day, with a starting dose of 30 mg/day) for at least 6 consecutive weeks. One hundred sixty-one outpatients were then randomized in a double-blind fashion, to either the same dose of ABILIFY they were on at the end of the stabilization and maintenance period or placebo and were then monitored for manic or depressive relapse. During the randomization phase, ABILIFY was superior to placebo on time to the number of combined affective relapses (manic plus depressive), the primary outcome measure for this study. The majority of these relapses were due to manic rather than depressive symptoms. There is insufficient data to know whether ABILIFY is effective in delaying the time to occurrence of depression in patients with bipolar I disorder.

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.

### ***Pediatric Patients***

The efficacy of ABILIFY in the treatment of bipolar I disorder in pediatric patients (10 to 17 years of age) was evaluated in one four-week placebo-controlled trial (n=296) of outpatients who met DSM-IV criteria for bipolar I disorder manic or mixed episodes with or without psychotic features and had a Y-MRS score  $\geq 20$  at baseline. This double-blind, placebo-controlled trial compared two fixed doses of ABILIFY (10 mg/day or 30 mg/day) to placebo. The ABILIFY dose was started at 2 mg/day, which was titrated to 5 mg/day after 2 days, and to the target dose in 5 days in the 10 mg/day treatment arm and in 13 days in the 30 mg/day treatment arm. Both doses of ABILIFY were superior to placebo in change from baseline to week 4 on the Y-MRS total score. Although maintenance efficacy in pediatric patients has not been systematically evaluated, maintenance efficacy can be extrapolated from adult data along with comparisons of aripiprazole pharmacokinetic parameters in adult and pediatric patients.

### **Adjunctive Therapy**

The efficacy of adjunctive ABILIFY with concomitant lithium or valproate in the treatment of manic or mixed episodes was established in a 6-week, placebo-controlled study (n=384) with a 2-week lead-in mood stabilizer monotherapy phase in adult patients

who met DSM-IV criteria for bipolar I disorder. This study included patients with manic or mixed episodes and with or without psychotic features.

Patients were initiated on open-label lithium (0.6 mEq/L to 1.0 mEq/L) or valproate (50 µg/mL to 125 µg/mL) at therapeutic serum levels, and remained on stable doses for 2 weeks. At the end of 2 weeks, patients demonstrating inadequate response (Y-MRS total score  $\geq 16$  and  $\leq 25\%$  improvement on the Y-MRS total score) to lithium or valproate were randomized to receive either aripiprazole (15 mg/day or an increase to 30 mg/day as early as day 7) or placebo as adjunctive therapy with open-label lithium or valproate. In the 6-week placebo-controlled phase, adjunctive ABILIFY starting at 15 mg/day with concomitant lithium or valproate (in a therapeutic range of 0.6 mEq/L to 1.0 mEq/L or 50 µg/mL to 125 µg/mL, respectively) was superior to lithium or valproate with adjunctive placebo in the reduction of the Y-MRS total score and CGI-BP Severity of Illness score (mania). Seventy-one percent of the patients coadministered valproate and 62% of the patients coadministered lithium were on 15 mg/day at 6-week endpoint.

Although the efficacy of adjunctive ABILIFY with concomitant lithium or valproate in the treatment of manic or mixed episodes in pediatric patients has not been systematically evaluated, such efficacy can be extrapolated from adult data along with comparisons of aripiprazole pharmacokinetic parameters in adult and pediatric patients.

### **14.3 Adjunctive Treatment of Major Depressive Disorder**

#### ***Adults***

The efficacy of ABILIFY in the adjunctive treatment of major depressive disorder (MDD) was demonstrated in two short-term (6-week), placebo-controlled trials of adult patients meeting DSM-IV criteria for MDD who had had an inadequate response to prior antidepressant therapy (1 to 3 courses) in the current episode and who had also demonstrated an inadequate response to 8 weeks of prospective antidepressant therapy (paroxetine controlled-release, venlafaxine extended-release, fluoxetine, escitalopram, or sertraline). Inadequate response for prospective treatment was defined as less than 50% improvement on the 17-item version of the Hamilton Depression Rating Scale (HAM-D17), minimal HAM-D17 score of 14, and a Clinical Global Impressions Improvement rating of no better than minimal improvement. Inadequate response to prior treatment was defined as less than 50% improvement as perceived by the patient after a minimum of 6 weeks of antidepressant therapy at or above the minimal effective dose.

The primary instrument used for assessing depressive symptoms was the Montgomery-Asberg Depression Rating Scale (MADRS), a 10-item clinician-rated scale used to assess the degree of depressive symptomatology (apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts). The key secondary instrument was the Sheehan Disability Scale (SDS), a 3-item self-rated instrument used to assess the impact of depression on three domains of functioning (work/school, social life, and family life) with each item scored from 0 (not at all) to 10 (extreme).

In the two trials (n=381, n=362), ABILIFY was superior to placebo in reducing mean MADRS total scores. In one study, ABILIFY was also superior to placebo in reducing the mean SDS score.

In both trials, patients received ABILIFY adjunctive to antidepressants at a dose of 5 mg/day. Based on tolerability and efficacy, doses could be adjusted by 5 mg increments, one week apart. Allowable doses were: 2 mg/day, 5 mg/day, 10 mg/day, 15 mg/day, and for patients who were not on potent CYP2D6 inhibitors fluoxetine and paroxetine, 20 mg/day. The mean final dose at the end point for the two trials was 10.7 mg/day and 11.4 mg/day.

An examination of population subgroups did not reveal evidence of differential response based on age, choice of prospective antidepressant, or race. With regard to gender, a smaller mean reduction on the MADRS total score was seen in males than in females.

## **14.4 Irritability Associated with Autistic Disorder**

### ***Pediatric Patients***

The efficacy of ABILIFY (aripiprazole) in the treatment of irritability associated with autistic disorder was established in two 8-week, placebo-controlled trials in pediatric patients (6 to 17 years of age) who met the DSM-IV criteria for autistic disorder and demonstrated behaviors such as tantrums, aggression, self-injurious behavior, or a combination of these problems. Over 75% of these subjects were under 13 years of age.

Efficacy was evaluated using two assessment scales: the Aberrant Behavior Checklist (ABC) and the Clinical Global Impression-Improvement (CGI-I) scale. The primary outcome measure in both trials was the change from baseline to endpoint in the Irritability subscale of the ABC (ABC-I). The ABC-I subscale measured the emotional

and behavioral symptoms of irritability in autistic disorder, including aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods.

The results of these trials are as follows:

In one of the 8-week, placebo-controlled trials, children and adolescents with autistic disorder (n=98), aged 6 to 17 years, received daily doses of placebo or ABILIFY 2 mg/day to 15 mg/day. ABILIFY, starting at 2 mg/day with increases allowed up to 15 mg/day based on clinical response, significantly improved scores on the ABC-I subscale and on the CGI-I scale compared with placebo. The mean daily dose of ABILIFY at the end of 8-week treatment was 8.6 mg/day.

In the other 8-week, placebo-controlled trial in children and adolescents with autistic disorder (n=218), aged 6 to 17 years, three fixed doses of ABILIFY (5 mg/day, 10 mg/day, or 15 mg/day) were compared to placebo. ABILIFY dosing started at 2 mg/day and was increased to 5 mg/day after one week. After a second week, it was increased to 10 mg/day for patients in the 10 mg and 15 mg dose arms, and after a third week, it was increased to 15 mg/day in the 15 mg/day treatment arm. All three doses of ABILIFY significantly improved scores on the ABC-I subscale compared with placebo.

## **14.5 Agitation Associated with Schizophrenia or Bipolar Mania**

The efficacy of intramuscular aripiprazole for injection for the treatment of agitation was established in three short-term (24-hour), placebo-controlled trials in agitated inpatients from two diagnostic groups: schizophrenia and bipolar I disorder (manic or mixed episodes, with or without psychotic features). Each of the trials included a single active comparator treatment arm of either haloperidol injection (schizophrenia studies) or lorazepam injection (bipolar mania study). Patients could receive up to three injections during the 24-hour treatment periods; however, patients could not receive the second injection until after the initial 2-hour period when the primary efficacy measure was assessed. Patients enrolled in the trials needed to be: (1) judged by the clinical investigators as clinically agitated and clinically appropriate candidates for treatment with intramuscular medication, and (2) exhibiting a level of agitation that met or exceeded a threshold score of  $\geq 15$  on the five items comprising the Positive and Negative Syndrome Scale (PANSS) Excited Component (ie, poor impulse control, tension, hostility,

uncooperativeness, and excitement items) with at least two individual item scores  $\geq 4$  using a 1-7 scoring system (1 = absent, 4 = moderate, 7 = extreme). In the studies, the mean baseline PANSS Excited Component score was 19, with scores ranging from 15 to 34 (out of a maximum score of 35), thus suggesting predominantly moderate levels of agitation with some patients experiencing mild or severe levels of agitation. The primary efficacy measure used for assessing agitation signs and symptoms in these trials was the change from baseline in the PANSS Excited Component at 2 hours post-injection. A key secondary measure was the Clinical Global Impression of Improvement (CGI-I) Scale. The results of the trials follow:

In a placebo-controlled trial in agitated inpatients predominantly meeting DSM-IV criteria for schizophrenia (n=350), four fixed aripiprazole injection doses of 1 mg, 5.25 mg, 9.75 mg, and 15 mg were evaluated. At 2 hours post-injection, the 5.25 mg, 9.75 mg, and 15 mg doses were statistically superior to placebo in the PANSS Excited Component and on the CGI-I Scale.

In a second placebo-controlled trial in agitated inpatients predominantly meeting DSM-IV criteria for schizophrenia (n=445), one fixed aripiprazole injection dose of 9.75 mg was evaluated. At 2 hours post-injection, aripiprazole for injection was statistically superior to placebo in the PANSS Excited Component and on the CGI-I Scale.

In a placebo-controlled trial in agitated inpatients meeting DSM-IV criteria for bipolar I disorder (manic or mixed) (n=291), two fixed aripiprazole injection doses of 9.75 mg and 15 mg were evaluated. At 2 hours post-injection, both doses were statistically superior to placebo in the PANSS Excited Component.

Examination of population subsets (age, race, and gender) did not reveal any differential responsiveness on the basis of these subgroupings.

## **16 HOW SUPPLIED/STORAGE AND HANDLING**

### **16.1 How Supplied**

ABILIFY<sup>®</sup> (aripiprazole) Tablets have markings on one side and are available in the strengths and packages listed in Table 15.

**Table 15: ABILIFY Tablet Presentations**

<b>Tablet Strength</b>	<b>Tablet Color/Shape</b>	<b>Tablet Markings</b>	<b>Pack Size</b>	<b>NDC Code</b>
<b>2 mg</b>	green modified rectangle	"A-006" and "2"	Bottle of 30	59148-006-13
<b>5 mg</b>	blue modified rectangle	"A-007" and "5"	Bottle of 30 Blister of 100	59148-007-13 59148-007-35
<b>10 mg</b>	pink modified rectangle	"A-008" and "10"	Bottle of 30 Blister of 100	59148-008-13 59148-008-35
<b>15 mg</b>	yellow round	"A-009" and "15"	Bottle of 30 Blister of 100	59148-009-13 59148-009-35
<b>20 mg</b>	white round	"A-010" and "20"	Bottle of 30 Blister of 100	59148-010-13 59148-010-35
<b>30 mg</b>	pink round	"A-011" and "30"	Bottle of 30 Blister of 100	59148-011-13 59148-011-35

ABILIFY DISCMELT<sup>®</sup> (aripiprazole) Orally Disintegrating Tablets are round tablets with markings on either side. ABILIFY DISCMELT is available in the strengths and packages listed in Table 16.

**Table 16: ABILIFY DISCMELT Orally Disintegrating Tablet Presentations**

<b>Tablet Strength</b>	<b>Tablet Color</b>	<b>Tablet Markings</b>	<b>Pack Size</b>	<b>NDC Code</b>
<b>10 mg</b>	pink (with scattered specks)	"A" and "640" "10"	Blister of 30	59148-640-23
<b>15 mg</b>	yellow (with scattered specks)	"A" and "641" "15"	Blister of 30	59148-641-23

ABILIFY<sup>®</sup> (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 59148-013-15

ABILIFY<sup>®</sup> (aripiprazole) Injection for intramuscular use is available as a ready-to-use, 9.75 mg/1.3 mL (7.5 mg/mL) solution in clear, Type 1 glass vials as follows:

9.75 mg/1.3 mL single-dose vial      NDC 59148-016-65

## 16.2 Storage

### Tablets

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

### Oral Solution

Store at 25° C (77° F); excursions permitted between 15° C to 30° C (59° F to 86° F) [see USP Controlled Room Temperature]. Opened bottles of ABILIFY Oral Solution can be used for up to 6 months after opening, but not beyond the expiration date on the bottle. The bottle and its contents should be discarded after the expiration date.

### Injection

Store at 25° C (77° F); excursions permitted between 15° C to 30° C (59° F to 86° F) [see USP Controlled Room Temperature]. Protect from light by storing in the original container. Retain in carton until time of use.

## 17 PATIENT COUNSELING INFORMATION

*See Medication Guide*

### 17.1 Information for Patients

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

#### **Increased Mortality in Elderly Patients with Dementia-Related Psychosis**

Patients and caregivers should be advised that elderly patients with dementia-related psychoses treated with antipsychotic drugs are at increased risk of death. ABILIFY is not approved for elderly patients with dementia-related psychosis [*see WARNINGS AND PRECAUTIONS (5.1)*].

#### **Clinical Worsening of Depression and Suicide Risk**

Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania,

other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to look for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication [*see WARNINGS AND PRECAUTIONS (5.2)*].

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with ABILIFY and should counsel them in its appropriate use. A patient Medication Guide about “Antidepressant Medicines, Depression and other Serious Mental Illness, and Suicidal Thoughts or Actions” is available for ABILIFY. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. It should be noted that ABILIFY is not approved as a single agent for treatment of depression and has not been evaluated in pediatric major depressive disorder.

### **Use of Orally Disintegrating Tablet**

Do not open the blister until ready to administer. For single tablet removal, open the package and peel back the foil on the blister to expose the tablet. Do not push the tablet through the foil because this could damage the tablet. Immediately upon opening the blister, using dry hands, remove the tablet and place the entire ABILIFY DISCMELT Orally Disintegrating Tablet on the tongue. Tablet disintegration occurs rapidly in saliva. It is recommended that ABILIFY DISCMELT be taken without liquid. However, if needed, it can be taken with liquid. Do not attempt to split the tablet.

### **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 [*see WARNINGS AND PRECAUTIONS (5.8)*].

## **Pregnancy**

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy with ABILIFY [*see USE IN SPECIFIC POPULATIONS (8.1)*].

## **Nursing**

Patients should be advised not to breast-feed an infant if they are taking ABILIFY [*see USE IN SPECIFIC POPULATIONS (8.3)*].

## **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 [*see DRUG INTERACTIONS (7)*].

## **Alcohol**

Patients should be advised to avoid alcohol while taking ABILIFY [*see DRUG INTERACTIONS (7.2)*].

## **Heat Exposure and Dehydration**

Patients should be advised regarding appropriate care in avoiding overheating and dehydration [*see WARNINGS AND PRECAUTIONS (5.9)*].

## **Sugar Content**

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

## **Phenylketonurics**

Phenylalanine is a component of aspartame. Each ABILIFY DISCMELT Orally Disintegrating Tablet contains the following amounts: 10 mg - 1.12 mg phenylalanine and 15 mg - 1.68 mg phenylalanine.

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

Orally Disintegrating Tablets, Oral Solution, and Injection 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: 5,006,528; 6,977,257; and 7,115,587

ABILIFY is a trademark of Otsuka Pharmaceutical Company.



**Bristol-Myers Squibb**



Otsuka

Otsuka America Pharmaceutical, Inc.

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Rev Month/2009

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## MEDICATION GUIDE

### ABILIFY<sup>®</sup> (a BIL ĭ fĭ)

Generic name: aripiprazole

#### **Antidepressant Medicines, Depression and other Serious Mental Illnesses, and Suicidal Thoughts or Actions**

Read the Medication Guide that comes with your or your family member's antidepressant medicine. This Medication Guide is only about the risk of suicidal thoughts and actions with antidepressant medicines. **Talk to your, or your family member's, healthcare provider about:**

- all risks and benefits of treatment with antidepressant medicines
- all treatment choices for depression or other serious mental illness

**What is the most important information I should know about antidepressant medicines, depression and other serious mental illnesses, and suicidal thoughts or actions?**

- 1. Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, and young adults within the first few months of treatment.**
- 2. Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a particularly high risk of having suicidal thoughts or actions.** These include people who have (or have a family history of) bipolar illness (also called manic-depressive illness) or suicidal thoughts or actions.

### **3. How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?**

- Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.
- Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
- Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare provider between visits as needed, especially if you have concerns about symptoms.

**Call a healthcare provider right away if you or your family member has any of the following symptoms, especially if they are new, worse, or worry you:**

- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- feeling very agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

### **What else do I need to know about antidepressant medicines?**

- **Never stop an antidepressant medicine without first talking to a healthcare provider.** Stopping an antidepressant medicine suddenly can cause other symptoms.
- **Antidepressants are medicines used to treat depression and other illnesses.** It is important to discuss all the risks of treating depression and also the risks of not treating it.

Patients and their families or other caregivers should discuss all treatment choices with the healthcare provider, not just the use of antidepressants.

- **Antidepressant medicines have other side effects.** Talk to the healthcare provider about the side effects of the medicine prescribed for you or your family member.
- **Antidepressant medicines can interact with other medicines.** Know all of the medicines that you or your family member takes. Keep a list of all medicines to show the healthcare provider. Do not start new medicines without first checking with your healthcare provider.
- **Not all antidepressant medicines prescribed for children are FDA approved for use in children.** Talk to your child's healthcare provider for more information.

This Medication Guide has been approved by the U.S. Food and Drug Administration for all antidepressants.

It should be noted that ABILIFY is approved to be added to an antidepressant when the response from the antidepressant alone is not adequate. ABILIFY is not approved for pediatric patients with depression.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

ABILIFY is a trademark of Otsuka Pharmaceutical Company.



**Bristol-Myers Squibb**



Otsuka

Otsuka America Pharmaceutical, Inc.

XXXXXXXXXX

XXXXX-XXXX

Rev Month/2009

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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 21-436/S027**

**OFFICER/EMPLOYEE LIST**

**Officer/ Employee List**  
**Application: NDA 021436/ S-027; ABILIFY (aripiprazole)**

The following officers/ or employees of FDA participated in the decision to approve this application and have consented to be identified:

Laughren, Thomas  
Pinto, Julia  
Mathis, Mitch  
Yang, Peiling  
Zhang, Jing

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 21-436/S027**

**OFFICE DIRECTOR MEMO**

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

**DATE:** November 19, 2009

**FROM:** Thomas P. Laughren, M.D.  
Director, Division of Psychiatry Products  
HFD-130

**SUBJECT:** Recommendation for approval action for Abilify in the treatment of irritability associated with autistic disorder

**TO:** File NDAs 21-436/S-027 (Abilify tabs)  
[Note: This overview should be filed with the 1-21-09 original submission of this supplement.]

**1.0 BACKGROUND**

Abilify (aripiprazole) is an atypical antipsychotic (5HT<sub>2</sub> antagonist and D<sub>2</sub> receptor partial agonist) that is approved for schizophrenia and bipolar disorder in both adults and pediatric patients (mania and mixed episodes), both acute and maintenance therapy for both. It is also approved as adjunctive therapy in MDD. S-027 was submitted in support of a new claim in the treatment of irritability associated with autistic disorder. Only one other drug, Risperdal, is currently approved for this indication. This new claim is supported by results from two 8-week aripiprazole studies in this population (CN138178 and CN138179). This new indication was developed under IND 71,501. Two meetings were held with the sponsor, including an EOP2 meeting (12-7-04) and a guidance meeting (1-17-07). We also corresponded on several occasions regarding the development plans and analysis plans. The clinical review was conducted by Jing Zhang, M.D., and the statistical review by Steve Bai. We did not take this application to the PDAC.

**2.0 CHEMISTRY**

The only CMC issues requiring review was the issue of environmental assessment. The sponsor sought and was granted a categorical exclusion.

### **3.0 PHARMACOLOGY**

There were no pharm/tox issues for review.

### **4.0 BIOPHARMACEUTICS**

Pediatric PK data were reviewed with the pediatric supplements for this drug, and these data are considered to support this expanded indication. Thus, there were no new PK data needing OCP review.

### **5.0 CLINICAL DATA**

#### **5.1 Efficacy Data**

Our efficacy review focused on two 8-week, placebo-controlled, multicenter (all US sites), double-blind, parallel group, randomized, efficacy and safety studies in pediatric patients (ages 6-17) with irritability (irritability, agitation, and self-injurious behavior) associated with autistic disorder (Studies CN138178 and CN138179). These studies were identical in design except that one was flexible dose (CN138178) and one was fixed dose (CN138179). The primary endpoint was mean change from baseline to endpoint on the Irritability Subscale of the ABC. The key secondary endpoint was the mean CGI-I at week 8.

##### **5.1.1 Study CN138178**

This was a flexible dose study (aripiprazole 2-15 mg/day). The mean dose at endpoint was 8.5 mg/day. The primary analysis was ANCOVA for the LOCF dataset. The results significantly favored aripiprazole over placebo on both the Irritability Subscale (5.0 improvement for placebo vs 12.9 improvement for aripiprazole;  $P < 0.0001$ ) and the CGI-I (3.6 vs 2.2;  $P < 0.0001$ ).

##### **5.1.2 Study CN138178**

This was a fixed dose study (aripiprazole 5, 10, and 15 mg/day). The primary analysis was ANCOVA for the LOCF dataset, with the Hochberg procedure for adjusting for multiplicity. The results significantly favored aripiprazole over placebo on both the Irritability Subscale (7.9 improvement for placebo vs 12.6, 12.9, and 14.5 improvement for aripiprazole 5, 10, and 15 mg/day, respectively;  $P = 0.0319$ ,  $0.0078$ , and  $0.0015$ , respectively). Results also statistically favored aripiprazole at all 3 doses over placebo on the CGI-I.

##### **5.1.2 Conclusions for Efficacy**

There is unanimous agreement within the review team on the positive outcome for these studies. We will request a maintenance study for phase 4.

## **5.2 Safety Data**

Safety data for this supplement were derived from the 2 trials noted above, plus an open label extension study in this population (CN138180), plus an aggregated data base of all pediatric studies (n=920, including 362 patients with autistic disorder). Overall, the profile of common and drug-related adverse events for patients with autistic disorder included events already well-recognized for aripiprazole in other pediatric populations, i.e., EPS, somnolence, and GI symptoms. There was a slightly greater finding of weight gain in the autistic population compared to the schizophrenia and bipolar pediatric populations. Of note, there were no other clear metabolic or growth effects, no laboratory effects, and if anything, a decrease in QTc. I agree with Dr. Zhang that these adverse events can be adequately addressed in labeling.

## **5.3 Clinical Sections of Labeling**

We made a number of modifications to the sponsor's proposed labeling, and have now reached agreement with the sponsor on final labeling.

## **6.0 WORLD LITERATURE**

The sponsor provided an extensive literature review and this did not reveal any important new safety information regarding the pediatric population.

## **7.0 FOREIGN REGULATORY ACTIONS**

To my knowledge, aripiprazole is not approved anywhere at this time for the treatment of irritability associated with autistic disorder.

## **8.0 DSI INSPECTIONS**

Inspections were conducted at 4 sites, and data from these sites were deemed to be acceptable.

## **9.0 LABELING AND APPROVAL LETTER**

### **9.1 Labeling**

We have included the agreed upon final labeling with the approval letter.

### **9.2 Foreign Labeling**

Aripiprazole is not approved anywhere at this time for the treatment of irritability associated with autistic disorder.

### **9.3 Approval Letter**

The approval letter includes the agreed upon labeling and the requirement for a maintenance study post-approval.

### **10.0 CONCLUSIONS AND RECOMMENDATIONS**

I believe that Otsuka has submitted sufficient data to support the conclusion that aripiprazole is effective and acceptably safe in the treatment of irritability associated with autistic disorder. We have reached agreement on final labeling and we will issue an approval letter.

cc:

Orig NDA 21-436/S-027 (Abilify tabs)

HFD-130/TLaughren/MMathis/JZhang/KAnsah

DOC: Aripiprazole\_Autism\_Laughren\_AP\_Memo.doc

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-21436

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SUPPL-27

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OTSUKA  
PHARMACEUTICA  
L CO LTD

-----  
ABILIFY (ARIPRAZOLE)  
10/15/20/30MG

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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THOMAS P LAUGHREN  
11/19/2009

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 21-436/S027**

**MEDICAL REVIEW(S)**

## CLINICAL REVIEW

Application Type sNDA  
Application Number(s) 21-436/027  
Priority or Standard S

Submit Date(s) 21 January 2009  
Received Date(s) 22 January 2009  
PDUFA Goal Date 21 November 2009  
Division / Office DPP/ONE1

Reviewer Name(s) Jing Zhang, MD., PhD.  
Review Completion Date October 30, 2009

Established Name Aripiprazole  
(Proposed) Trade Name Abilify®  
Therapeutic Class Atypical Antipsychotic  
Applicant Otsuka Pharmaceutical Co,  
Ltd

Formulation(s) 2, 5, 10, & 15 mg tablets  
Dosing Regimen 2 to 15 mg  
Indication(s) Irritability Associated with  
Autistic Disorder  
Intended Population(s) 6 to 17 year old

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## **1 Recommendations/Risk Benefit Assessment**

### **1.1 Recommendation on Regulatory Action**

Otsuka submitted this sNDA intended to seek for a new indication of aripiprazole in the treatment of irritability associated with autistic disorder. Based on the available data submitted to this supplemental NDA, mainly obtained from two 8-week, double-blind, placebo-controlled studies, it is recommended that this NDA be granted an approval status.

Several labeling recommendations have been made. Please refer to section 9.2 Labeling Recommendations for detailed recommendations. Final approval is contingent on satisfactory response to the agency's recommendations and mutual agreement on labeling as well as the conclusions of the CMC, pharmacology/toxicology, and clinical pharmacology reviewers.

### **1.2 Risk Benefit Assessment**

Autistic disorder is a neurodevelopmental disorder characterized by abnormalities in social interaction, communication, and the presence of restricted and repetitive behaviors. There are many secondary behavioral features that are commonly associated with autism. These include irritability and tantrums, attention and/or hyperactivity disorders, self-injury, odd responses to sensory stimuli, lack of fear or excessive fearfulness, and many others. Many of these can profoundly impair functioning and cause substantial individual and family burden. Reducing symptom burden as much as possible is a commonly accepted therapeutic goal. Risperdal is an only approved medication for treating pediatric patients with irritability associated with autistic disorder. Alternative treatment options would be necessary.

The efficacy of aripiprazole in improving symptoms of irritability in children and adolescents with autistic disorder was demonstrated by positive results obtained from two 8-week, randomized, multicenter, double-blind, placebo-controlled studies (CN138178 and CN138179). The safety evaluation demonstrated that the safety profile of aripiprazole in autistic population is similar to that obtained from pediatric schizophrenic and bipolar populations. Aripiprazole was generally safe and well tolerated in this population.

Given irritability associated with autistic disorder is a serious psychiatric condition, and Risperdal is the only drug approved in the USA for this condition, it is believed that the benefit of having aripiprazole available for this psychiatric condition justifies the risk of potential adverse events with aripiprazole treatment.

### **1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies**

The safety profile of aripiprazole in pediatric autistic population is comparable to that obtained from pediatric schizophrenic and bipolar population. No specific safety concern had been identified from this submission. Risk Evaluation and Mitigation Strategies are not required at this time.

### **1.4 Recommendations for Postmarket Requirements and Commitments**

The division requested BMS/Otsuka conduct a long-term maintenance study as a Post-market Commitment to assess the long-term efficacy and safety of aripiprazole in autistic patients ages 6 to 16 with a history of irritability. BMS/Otsuka had committed to conduct this study. The protocol for this study will be submitted 6 months post approval and initiated 1 year post approval. Study completion is anticipated 3 years after study start with a clinical study report submission 1 year after the study is completed.

## **2 Introduction and Regulatory Background**

### **2.1 Product Information**

Aripiprazole is a dopamine presynaptic D<sub>2</sub> auto-receptor partial agonist and belongs to atypical antipsychotic family. Same as other atypical antipsychotics, aripiprazole also acts as an antagonist at serotonin 5-HT<sub>1A</sub> receptor.

ABILIFY<sup>®</sup> (aripiprazole) is approved for the treatment of schizophrenia and acute manic or mixed episodes associated with bipolar I disorder in adults in the United States (US, the European Union (EU), and several other countries. ABILIFY is also approved in the US as adjunctive treatment in adult patients with major depressive disorder. In pediatric patients, ABILIFY is approved in the US for the treatment of schizophrenia in adolescents (ages 13-17) and in children and adolescents (ages 10-17) with bipolar I disorder.

### **2.2 Tables of Currently Available Treatments for Proposed Indications**

Risperdal is the only medication that has been approved in the USA for the indication of irritability associated with autistic disorder.

### **2.3 Availability of Proposed Active Ingredient in the United States**

Aripiprazole is an approved drug in the United States.

## **2.4 Important Safety Issues With Consideration to Related Drugs**

Aripiprazole is an atypical antipsychotic. However, aripiprazole has a unique dopamine D<sub>2</sub> receptor partial agonist property. As a member of atypical antipsychotics, aripiprazole labeling carries same class warnings and precautions as other atypical antipsychotics. No important issues with pharmacologically related products were identified from this submission.

## **2.5 Summary of Presubmission Regulatory Activity Related to Submission**

07-Dec-2004	EOP2 meeting to discuss the registrational plan for treatment of serious behavior problems associated with autism
08-Apr-2005	Initial IND (IND 71,501) submission
08-Jun-2005	FDA letter in response to BMS request for special protocol assessment (CN138-178, -179, and -180)
25-Jul-2005	FDA statistical comments on CN138-178, and -179
17-Jan-2007	Met with FDA for a guidance meeting for autistic disorder program
08-Feb-2008	Statistical Analysis Plan for CN138-178 submitted
06-May-2008	Statistical Plan Updates for CN138-178 and -179 submitted
08-Aug-2008	Background Document for pre-sNDA meeting submitted
09-Sep-2008	Pre-sNDA meeting cancelled

## **2.6 Other Relevant Background Information**

Aripiprazole has not been withdrawn from the market worldwide for any reason.

# **3 Ethics and Good Clinical Practices**

## **3.1 Submission Quality and Integrity**

During the course of the review, no problems with respect to data quality or integrity were identified.

The division of scientific investigation inspected 4 study sites: Dr. Melmed (Phoenix, AZ); Dr. Attala (Smyrna, GA); Dr. Hardan (Stanford, CA); and Dr. Rugino (Toms River, NJ). Anthony Orescia, MD., is the primary medical officer for this submission. Please refer to his clinical inspection summary of detailed pertinent information. The inspection did not find significant discrepancies with the data listings provided in the NDA and source documents at the clinical sites and concluded that the data generated by these sites appear reliable in support of the application.

### 3.2 Compliance with Good Clinical Practices

Study CN138-178 and CN138-179 were performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with ICH/Good Clinical Practice and applicable regulatory requirements.

### 3.3 Financial Disclosures

(b) (6) who has participated in study (b) (6), received significant payments of other sorts made on or after February 2, 1999 from the sponsor such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria. (b) (6) site has enrolled (b) (6) patients and (b) (6) of them were randomized.

(b) (6) who has participated in study (b) (6) might have received less than \$25,000 from (b) (6) for giving speeches. (b) (6) site has enrolled (b) (6) patients and (b) (6) of them were randomized.

Both studies are multi-center, double-blinded studies. Thus, it is less likely that aforementioned arrangements have biased the study results.

## 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

### 4.1 Chemistry Manufacturing and Controls

There is no new CMC information provided in this submission. The Sponsor has requested a categorical exclusion from the preparation of an environmental assessment, under 21 CFR 25.31 (a), based on an estimate that the concentration of the active moiety in the environment will remain at less than 1 ppb, regardless of the potential increase in use, due to the additional indication. The CMC reviewer, Julia C.

Pinto, PhD, has no objection to the sponsor's exclusion request. No environmental assessment is required for this submission.

#### **4.2 Clinical Microbiology**

No clinical microbiology study was deemed necessary.

#### **4.3 Preclinical Pharmacology/Toxicology**

No preclinical pharmacology/toxicology study was submitted to this sNDA.

#### **4.4 Clinical Pharmacology**

No PK/PD or drug-drug interaction studies was submitted to this sNDA.

### **5 Sources of Clinical Data**

#### **5.1 Tables of Studies/Clinical Trials**

Table 1 summarizes the aripiprazole autistic disorder clinical program.

**Table 1 Aripiprazole Autistic Disorder Clinical Program**

Study Number	Number of Study Centers/ Location/ Study Dates	Design	Study Objective	Study Drugs	Randomized/ Treated	Gender/ Mean Age (Range)	Endpoints
<b>Short-term Placebo-controlled Studies</b>							
CN138178	18 US centers <sup>a</sup> / 6/06 - 4/08	Phase 3: Randomized, double-blind study comparing flexibly-dosed aripiprazole with placebo for 8 weeks	Efficacy and Safety	Aripiprazole flexibly dosed (2 - 15mg) Placebo	47/47  51/50	86 Males 12 Females 9.3 years (6-17)	Primary Efficacy: Mean change from baseline to endpoint (Week 8) in ABC Irritability Subscale Score. Key Secondary Efficacy: mean CGI-Improvement Score Safety: AEs, EPS-related AEs, Simpson-Angus Scale, Abnormal Involuntary Movement Scale, Barnes Akathisia Rating Scale, laboratory tests, vital sign measurements, 12-lead ECGs
CN138179	31 US centers <sup>a</sup> / 6/06 - 6/08	Phase 3: Randomized, double-blind study comparing fixed-dose aripiprazole with placebo for 8 weeks	Efficacy and Safety	Aripiprazole 5 mg Aripiprazole 10 mg Aripiprazole 15 mg Placebo	53/52 59/59 54/54 52/51	195 Males 23 Females 9.7 years (6-17)	Primary Efficacy: Mean change from baseline to endpoint (Week 8) in ABC Irritability Subscale Score. Safety: AEs, EPS-related AEs, Simpson-Angus Scale, Abnormal Involuntary Movement Scale, Barnes Akathisia Rating Scale, laboratory tests, vital sign measurements, 12-lead ECGs
<b>Long-term Open-label Study</b>							
CN138180	49 US centers/ 6/06 - ongoing	Phase 3: Open-label study with flexibly-dosed aripiprazole for 52 weeks	Safety	Aripiprazole flexibly dosed (2-15mg)	347/313	274 Males 39 Females 9.8 years (6-17)	Safety: AEs, EPS-related AEs, Simpson-Angus Scale, Abnormal Involuntary Movement Scale, Barnes Akathisia Rating Scale, laboratory tests, vital sign measurements, 12-lead ECGs

## 5.2 Review Strategy

Material reviewed in this review cycle includes Clinical Study Reports from CN138-178 and CN138-179, Clinical Summaries, Clinical Overview, Safety Update, and the proposed labeling. The efficacy review was performed in consultation with the statistical reviewer, Steven Bai, PhD. Please refer to his review for more detailed pertinent efficacy information.

## 5.3 Discussion of Individual Studies/Clinical Trials

The aripiprazole autistic disorder program consisted of 2 placebo-controlled studies of identical design except that fixed dosing was used for one (CN138179) and flexible dosing for the other (CN138178). Both studies are positive studies—aripiprazole demonstrated superiority over placebo in the treatment of irritability in children and adolescents (aged 6 - 17 years) with autistic disorder. Aripiprazole was generally safe and well tolerated in this population. In addition, there is an open-label uncontrolled safety study (CN138180) currently ongoing.

## 6 Review of Efficacy

### A. Studies for the Indication of Irritability Associated with Autism Disorder

#### a. Rationale for Selection of Studies for Review

The autism program consisted of two 8-week, multi-center, double-blind, randomized, placebo-controlled efficacy studies of nearly identical design with the main exception that flexible dosing (5 to 15 mg) was used for one (CN138178) and fixed dosing (5, 10 and 15 mg) for the other (CN138179). For both studies, the primary endpoint is the mean change from baseline to Week 8 in the Aberrant Behavior Checklist (ABC) Irritability Subscale. There was a key secondary endpoint, the mean change from baseline to endpoint in Clinical Global Impressions Improvement (CGI-I) score in study CN138178. There was no key secondary endpoint in study CN138179. Both studies were positive studies and were reviewed in detail in this clinical review.

The ABC is an informant-based symptom checklist for assessing the classifying problem behaviors of children and adolescents with mental retardation. The 58 items are rated on a 4-point scale (0 = not at all a problem to 3 = the problem is severe in

degree), and resolve into 5 subscales: (1) irritability, agitation; (2) lethargy, social withdrawal; (3) stereotypic behavior; (4) hyperactivity, noncompliance; and (5) inappropriate speech. The ABC-Irritability Subscale consists of 15 items, each rated on a scale from 0 to 3, with a maximum score of 45. As a primary endpoint, ABC Irritability Subscale was used in Risperdal pediatric trials for the indication of irritability associated with autistic disorder. ABC Irritability Subscale had been accepted by the division as a valid measurement for irritability symptomatology in autistic patients.

The Clinical Global Impressions (CGI) Scale is a standardized assessment tool. Its goal is to allow the clinician to rate the severity of illness, change over time, and efficacy of medication, taking into account the patient's clinical condition and the severity of side effects. The CGI Scale is widely used in clinical psychopharmacology trials as an outcome measure. The measure had been accepted by the division as a reasonable secondary endpoint for many clinical trials.

## **b. Study Summaries**

### **Study CN138178**

#### *i. Method/Study Design/Analysis Plan*

Study CN138178 was conducted from 15 June 2006 to 28 April 2008 at 19 centers in the United States. A complete list of investigators, their staff, study centers, and number of patients enrolled per center are listed in Appendix 1.5 in the original sDNA submission.

#### Overall Study Design

Study CN138178 was a 8 week, multicenter, flexible-dose, double-blind, randomized, placebo-controlled, parallel-group study designed to assess the efficacy, safety, and tolerability of aripiprazole in children and adolescents with a DSM-IV diagnosis of autistic disorder with serious behavioral problems characterized by irritability, agitation, and self-injurious behavior.

This study had 2 phases: a screening phase of up to 42 days followed by an 8-week treatment phase. Eligible patients were randomized to treatment with either aripiprazole (2 to 15 mg/day) or placebo in a 1:1 ratio. Patients visited the clinic at the end of treatment Weeks 1, 2, 3, 4, 5, 6, and 8, at which time efficacy and safety measures were collected. To assess patient well-being and medication tolerability between visits in the latter half of the double-blind treatment phase, a telephone contact occurred at Week 7. End of study assessments were performed at the end of Week 8 or at the time

of early termination. Patients who completed the 8-week, double-blind treatment phase were eligible for an open-label long-term study.

Approximately 100 patients were planned to be randomly assigned to receive aripiprazole (2 to 15 mg) or placebo. A total of 164 patients were enrolled with 98 randomized (51 in the placebo group and 47 in the aripiprazole group).

#### Dose and Administration

A flexible dosing regimen was used for each patient. For all patients randomized to receive aripiprazole, the starting dose was 2 mg. Doses can be increased to 5, 10 or 15 mg based on clinical response and tolerability. The maximum possible dose was 15 mg. No dose increases were to occur after Visit 8 (Week 6). Ideally, the dose should remain stable during the final 2 weeks of treatment. If, at any time, the patient experienced intolerance to the current dose taken, the dosage could be adjusted downward.

Study medication was administered once daily beginning on Day 1. Doses were to be taken at approximately the same time each day without regard to meals.

#### Selection of Study Population

##### Key Inclusion Criteria:

- Male or female children or adolescents 6 to 17 years of age, inclusive, met current DSM-IV-TR diagnostic criteria for autistic disorder and also demonstrated behaviors such as tantrums, aggression, self-injurious behavior, or a combination of these problems. Diagnosis was confirmed by the Autism Diagnostic Interview—Revised.
- The patient had a CGI-S score  $\geq 4$  and an ABC Irritability Subscale score  $\geq 18$  at screening and baseline
- The patient and/or the designated guardian(s) or caregiver(s) were able to comprehend and satisfactorily comply with the protocol requirements, in the opinion of the investigator
- The patient had a documented mental age of at least 18 months
- Women of childbearing potential (WOCBP) had to use an adequate method of contraception to avoid pregnancy throughout the study and for up to 8 weeks after the study. WOCBP must have had a negative serum or urine pregnancy test.

Key Exclusion Criteria:

- The patient had a current diagnosis of bipolar disorder, psychosis, schizophrenia, or major depression
- The patient was currently diagnosed with another disorder on the autism spectrum including PDD-NOS, Asperger's Disorder, Rett's Disorder, Fragile-X Syndrome or Childhood Disintegrative Disorder
- The patient had a significant risk of committing suicide based on history or routine psychiatric status examination
- The patient had a history or current evidence of any unstable medical conditions (eg, history of congenital heart disease or arrhythmia, or cancer) that, in the judgment of the investigator, would expose him or her to undue risk of a significant adverse event (AE) or interfere with assessments of safety or efficacy during the course of the trial
- The patient was considered treatment resistant to neuroleptic medication, in the opinion of the investigator, based on lack of therapeutic response to 2 different neuroleptics after treatment of at least 3 weeks each
- The patient was considered treatment resistant to aripiprazole, in the opinion of the investigator, based on lack of therapeutic response to an adequate dose and duration of aripiprazole treatment
- Women who were pregnant or breastfeeding
- The following laboratory test results, vital sign and electrocardiogram (ECG) findings were exclusionary:
  - QTc > 475 msec
  - Platelets ≤ 75,000/mm<sup>3</sup>
  - Hemoglobin ≤ 9g/dL
  - Neutrophils ≤ 1.0 x E<sup>3</sup>/mm<sup>3</sup> (or equivalent)
  - Aspartate transaminase (AST) [serum glutamic-oxaloacetic transaminase (SGOT)] or alanine transaminase (ALT) [serum glutamic-pyruvic transaminase (SGPT)] > 3x upper limit of normal
  - Creatinine ≥ 2 mg/dL
- The patient weighed < 15 kg

- The patient had a known allergy or hypersensitivity to aripiprazole or other dihydrocarbostyrils (eg, carteolol, vesnarinone, and cilostazol)

### The Primary and Secondary Efficacy Endpoints

The primary efficacy outcome measure was the mean change from baseline to endpoint (Week 8) in the ABC Irritability Subscale score. The key secondary efficacy outcome measure was the mean CGI-I score. Other secondary efficacy outcome measures included the mean change from baseline to endpoint in the other ABC subscale scores, response rate (response defined as a  $\geq 25\%$  reduction from baseline to endpoint in the ABC Irritability Subscale score and a CGI-I score of 1 or 2 at endpoint), and mean change from baseline to endpoint in the Children's Yale-Brown Obsessive Compulsive Scale (CY-BOCS) (Compulsion Scale only).

### Statistical Methods

The sample size of 90 evaluable patients (45 per treatment group) was estimated to provide 93% power to differentiate between placebo and the aripiprazole treatment group when the true difference in the mean changes from baseline in the ABC Irritability Subscale score was 7.0. This assumed a standard deviation of 9.42 and a 2-sided test at the 0.05 level of significance.

The Randomized Sample included all patients who were randomized to double-blind treatment. The Safety Sample comprised all patients in the Randomized Sample who took at least 1 dose of study medication during the double-blind Treatment Phase, as identified on the dosing record. The Efficacy Sample comprised all patients who were in the Safety Sample and had at least 1 post-randomization efficacy evaluation and corresponding baseline value. The last observation carried forward (LOCF) data set included data recorded at a given timepoint or, if no observation was recorded at that timepoint, data carried forward from the previous timepoint with available data. Baseline data were not carried forward or averaged with the on-treatment data to impute missing values for the LOCF data set. The observed cases (OC) data set consisted of the actual observations at each timepoint.

For continuous measurements, such as the ABC Irritability Subscale score, change scores were evaluated by analysis of covariance (ANCOVA). The ANCOVA models for LOCF data sets included the baseline measure as a covariate and baseline body weight (2 categories:  $\geq 40$  kg and  $< 40$  kg), study center, and treatment as main effects.

Categorical measures such as response were analyzed within the framework of the generalized Cochran-Mantel Haenszel (CMH) procedure. The analyses of the LOCF data set controlled for study center.

P-values were 2-tailed tests of significance rounded to 3 decimal places. All analyses were performed at the 5% significance level. For the analysis of the key secondary efficacy endpoint, a hierarchical testing procedure was used in order to protect the overall experiment-wise type I error rate at 0.05. Thus, the CGI-I would be tested only if the aripiprazole treatment group was significantly different versus placebo from the primary efficacy endpoint analysis.

Safety and tolerability of study medication were evaluated by reports of AEs including clinically significant changes in ECGs, vital signs, physical examinations, and clinical laboratory tests. The incidence of AEs was tabulated by treatment, according to severity, and drug-attributability.

In addition, weight and body mass index (BMI) were also evaluated in terms of change from baseline. The analytical approaches described for the efficacy analyses were applied to the safety rating scales and weight/BMI evaluations.

All safety analyses were performed on the Safety Sample. For safety analyses, patients were analyzed by treatment received.

## ii. Results

### Demographics

Demographic characteristics for the Randomized Sample are presented in Table 2. The mean age of the randomized patients was 9.3 years (range 6 - 17 years). Patients were predominantly male (87.8%) and white (74.5%) which were consistent with the prevalence of autistic disorder (4-5 times more common in male than in female) and roughly consistent with the race distribution in the general population in the United States.

**Table 2 Demographic Characteristics, Randomized Sample, Study CN138178**

		Placebo (n=51)	Aripiprazole (n=47)	Total (n=98)
Age (years)	Mean	8.8	9.7	9.3
6-12	N (%)	46 (90.2)	37 (78.7)	83 (84.7)
13-17	N (%)	5 (9.8)	10 (21.3)	15 (15.3)
Gender				
Male	N (%)	44 (86.3)	42 (89.4)	86 (87.8)
Female	N (%)	7 (13.7)	5 (10.6)	12 (12.2)
Race				
White	N (%)	41 (80.4)	32 (68.1)	73 (74.5)
Black/African American	N (%)	7 (13.7)	11 (23.4)	18 (18.4)
Asian	N (%)	0	2 (4.3)	2 (2.0)
Other	N (%)	3 (5.9)	2 (4.3)	5 (5.1)

		Placebo (n=51)	Aripiprazole (n=47)	Total (n=98)
Weight (kg)	Mean	40.6	43.9	42.2
< 40 kg	N (%)	32 (62.7)	26 (55.3)	58 (59.2)
≥ 40 kg	N (%)	19 (37.3)	21 (44.7)	40 (40.8)
Height (cm)	Mean	138.6	140.9	139.7
BMI (kg/m <sup>2</sup> )	Mean	19.96	21.08	20.50

### Baseline Disease Characteristics

The ABC, CGI-S, and CY-BOCS ratings from the end of baseline are presented in Table 3. Mean baseline ratings were similar between treatment groups.

**Table 3 Baseline Disease Characteristics, Randomized Sample, Study CN138178**

Scale	Placebo N=51	Aripiprazole N=47	Total N=98
ABC, mean (SD)			
Irritability	30.2 (6.52)	29.6 (6.37)	29.9 (6.42)
Hyperactivity	35.3 (8.86)	34.0 (8.64)	34.7 (8.73)
Stereotypy	11.2 (5.79)	11.8 (6.13)	11.5 (5.93)
Social Withdrawal	18.8 (9.62)	19.9 (11.26)	19.3 (10.40)
Inappropriate Speech	6.8 (3.98)	6.9 (3.78)	6.8 (3.87)
CGI-Severity, mean (SD)	4.9 (0.63)	4.9 (0.71)	4.9 (0.67)
CY-BOCS, mean (SD)			
Compulsion	14.2 (3.39)	12.9 (4.94)	13.6 (4.24)

### Patient Disposition

A total of 164 patients were enrolled in the study. Of these, 98 patients were randomized to receive treatment: 51 patients to the placebo group and 47 patients to aripiprazole. A total of 75 (76.5%) of the 98 randomized patients completed the double-blind phase of the study, 36 (70.6%) in the placebo group and 39 (83.0%) in the aripiprazole group. Placebo treatment was associated with higher discontinuation rate. The most frequent reasons for discontinuation in the placebo group were lack of efficacy, 6 (11.8%) patients, and for the aripiprazole group was adverse events (AE), 5 (10.6%) patients.

The disposition of randomized patients is presented in Table 4.

**Table 4 Disposition of Patients, Study CN138178**

Patient Status	Placebo	Aripiprazole	Total
Randomized, n	51	47	98
Completed, n (%)	36 (70.6)	39 (83.0)	75 (76.5)
Discontinued, n (%)	15 (29.4)	8 (17.0)	23 (23.5)
Lack of efficacy	6 (11.8)	1 (2.1)	7 (7.1)
Adverse event	3 (5.9)	5 (10.6)	8 (8.2)
Subject withdrew consent	2 (3.9)	1 (2.1)	3 (3.1)
Lost to follow-up	4 (7.8)	1 (2.1)	5 (5.1)

All randomized patients were included in the Safety Sample except for 1 patient in the placebo group who was lost to follow-up (CN138178-1-78148). One additional patient in each treatment group was not included in the Efficacy Sample (placebo: CN138178-3-78001 withdrew consent to participate; aripiprazole: CN138178-13-78058 had an AE of severe vomiting that started Day 1, he discontinued from the study on Day 2).

#### Concomitant Medication Use

The most commonly used CNS concomitant medications during this study for placebo-treated and aripiprazole-treated patients were “other analgesics and antipyretics” (placebo 22.0%, aripiprazole 19.1%). Only a few of patients used other concomitant CNS medications during this study, such hypnotic & sedative (placebo 6 (12%); aripiprazole 1 (2.1%)), and anxiolytic (placebo 2 (4%); aripiprazole 4 (8.5%)). It is unlikely that the concomitant medication use during this study had affected the final efficacy outcome.

#### Protocol Deviations

Clinical relevant protocol deviations were identified during the study and were summarized in Table 5. No patient was excluded from the analyses because of a relevant protocol deviation.

**Table 5 Protocol Deviations of Clinical Relevance, Study CN138178**

Deviation	Number of Patients N=98 <sup>a</sup>
Randomized patients with missing vital signs at screening or baseline	22
Randomized patients with missing or exclusionary ECG result at screening or baseline	1
Randomized patients with concomitant prohibited or restricted medications	2
Treated patients with study medication not administered per protocol	3

## Efficacy Findings

### *Primary Efficacy Endpoint*

The primary endpoint was the mean change from baseline to Week 8 LOCF in the ABC Irritability Subscale score. There was a statistically significant difference between the treatment groups in favor of aripiprazole in the adjusted mean change from baseline to Week 8 LOCF in the ABC Irritability Subscale score (placebo -5.0, aripiprazole -12.9, difference -7.9, 95% CI (-11.7, -4.1),  $p < 0.001$ ) (Table 6). These results were corroborated by the OC data set (Table 7). Differences between treatment groups on this measure were statistically significant consistently from Week 1 onward.

**Table 6 Adjusted Mean Change from Baseline in ABC Irritability Subscale Score, Study CN138178, LOCF, Efficacy Sample**

Visit	Placebo		Aripiprazole		Arip. vs. PLA
	n	Mean (SE)	n	Mean (SE)	p-value
Baseline	49	30.8 (1.00)	46	29.6 (1.01)	0.372
Week 1	46	-2.7 (1.02)	45	-5.5 (1.01)	0.039
Week 2	49	-3.6 (1.13)	46	-8.5 (1.13)	0.002
Week 3	49	-4.6 (1.18)	46	-10.4 (1.19)	<0.001
Week 4	49	-6.6 (1.23)	46	-11.8 (1.24)	0.002
Week 5	49	-5.7 (1.35)	46	-12.0 (1.36)	<0.001
Week 6	49	-6.2 (1.43)	46	-13.2 (1.44)	<0.001
Week 8	49	-5.0 (1.43)	46	-12.9 (1.44)	<0.001
Week 8: Treatment difference vs. placebo and corresponding 95% CI					-7.9 (-11.7, -4.1)

**Table 7 Adjusted Mean Change from Baseline in ABC Irritability Subscale Score, Study CN138178, OC, Efficacy Sample**

Visit	Placebo		Aripiprazole		Arip. vs. PLA
	n	Mean (SE)	n	Mean (SE)	p-value
Baseline	49	30.6 (0.94)	46	29.6 (0.95)	0.435
Week 1	46	-2.5 (0.93)	45	-5.1 (0.92)	0.044
Week 2	46	-3.4 (1.01)	42	-8.8 (1.04)	<0.001
Week 3	43	-4.5 (1.10)	40	-10.8 (1.12)	<0.001
Week 4	39	-6.0 (1.19)	40	-12.0 (1.16)	<0.001
Week 5	40	-5.8 (1.30)	39	-12.9 (1.31)	<0.001
Week 6	38	-7.0 (1.47)	38	-14.6 (1.46)	<0.001
Week 8	34	-5.2 (1.49)	38	-14.5 (1.41)	<0.001
Week 8: Treatment difference vs. placebo and corresponding 95% CI					-9.2 (-13.3, -5.2)

### **iii. Conclusions**

In study CN138178, aripiprazole at dose of 2 to 15 mg/d demonstrated clinically relevant and statistically significant improvement compared with placebo on the primary efficacy endpoint, the adjusted mean change from baseline on the ABC Irritability Subscale, starting at Week 1 and continuing through endpoint (Week 8 LOCF).

The statistical reviewer, Steve Bai PhD., reanalyzed the data using both LOCF and MMRM analyses and confirmed the efficacy findings.

## **Study CN138179**

### **i. Method/Study Design/Analysis Plan**

Study CN138179 was conducted from 15 June 2006 to 03 June 2008 at 37 centers in the United States. A complete list of investigators, their staff, study centers, and number of patients enrolled per center are listed in Appendix 1.5 in the original DNA submission.

#### Overall Study Design

The study design of CN138179 was identical to that of study CN 138178 except study CN138179 was a fixed-dose study and CN138178 was a flexible-dose study.

Study CN138179 was a fixed-dose (5, 10 or 15 mg/d), double-blind, randomized, placebo-controlled, parallel-group, multicenter 8-week study designed to assess the efficacy, safety, and tolerability of aripiprazole in children and adolescents with a DSM-IV diagnosis of autistic disorder with serious behavioral problems characterized by irritability, agitation, and self-injurious behavior.

The study had 2 phases: a screening phase of up to 42 days followed by an 8-week treatment phase. Eligible Patients were randomized to treatment with aripiprazole 5 mg, 10 mg or 15 mg/day, or placebo in a 1:1:1:1 ratio. Patients visited the clinic at the end of treatment Weeks 1, 2, 3, 4, 5, 6, and 8, at which time efficacy and safety measures were collected. To assess patient well-being and medication tolerability between visits in the latter half of the double-blind treatment phase, a telephone contact occurred at Week 7. End of study assessments were performed at the end of Week 8 or at the time of early termination. Patients who completed the 8-week, double-blind treatment phase were eligible for an open-label, flexible-dosed, long-term study.

Approximately 220 patients were planned to be randomly assigned to receive aripiprazole (2, 5 or 15 mg/d) or placebo. A total of 368 patients were enrolled with 218 patients randomized to receive treatment: 52 received placebo; 53, 59, and 54 received aripiprazole 5, 10 and 15 mg respectively.

### Dose and Administration

A fixed dosing regimen was used for each patient. For all patients randomized to receive aripiprazole, the starting dose was 2 mg for the first week. All patients were titrated to their randomized dose at weekly increments in a blinded fashion. For example, a patient randomized to 15 mg took 2 mg the 1st week, 5 mg the 2nd week, 10 mg the 3rd week, 15 mg the 4th week, and continued on 15 mg for the remainder of the study. Patients unable to tolerate a dose to which they were randomized were discontinued from the study.

Study medication was administered once daily beginning on Day 1. Doses were to be taken at approximately the same time each day without regard to meals.

### Selection of Study Population

Key inclusion and exclusion criteria in study CN138179 were same as that in study CN138178. Please refer to section 6 *Review of Efficacy/Study CN138178/Selection of Study Population* for detailed key inclusion and exclusion criteria.

### The Primary and Secondary Efficacy Endpoints

The primary efficacy outcome measure was the mean change from baseline to endpoint (Week 8) in the ABC Irritability Subscale score. Secondary efficacy outcome measures included the mean change from baseline to endpoint in the CGI-I, the other ABC subscale scores, response rate (response defined as a  $\geq 25\%$  reduction from baseline to endpoint in the ABC Irritability Subscale score and a CGI-I score of 1 or 2 at endpoint), and mean change from baseline to endpoint in the CY-BOCS (Compulsion Scale only). No key secondary endpoint was pre-specified.

### Statistical Methods

The planned sample size of 240 evaluable patients (51 per treatment group) was estimated to provide 92% power to differentiate between placebo and at least 1 or 2 higher dosage aripiprazole treatment groups (10 or 15 mg/d) when the true difference in the mean changes from baseline in the ABC Irritability Subscale score was 7.0. This assumed a standard deviation of 9.42 and a 2-sided test at the 0.05 level of significance.

The rest of the statistical plan was same as that in study CN138178. Please refer to section 6 *Review of Efficacy/Study CN138178/Statistical Methods* for detailed statistical methods.

## ii. Results

### Demographics

Demographic characteristics for the Randomized Sample are presented in Table 8. The mean age of the randomized patients was 9.7 years. Patients were predominantly male (89.4%) and white (71.1%) which were consistent with the prevalence of autistic disorder (4-5 times more common in male than in female) and the race distribution in the general population in the United States.

**Table 8 Demographic Characteristics, Study CN138179, Randomized Sample**

		Placebo (n=52)	Aripiprazole 5 mg (n=53)	Aripiprazole 10 mg (n=59)	Aripiprazole 15 mg (n=54)	Total (n=218)
Age (years)	Mean	10.2	9.0	10.0	9.5	9.7
6-12	N (%)	35 (67.3)	44 (83.0)	45 (76.3)	42 (77.8)	166 (76.1)
13-17	N (%)	17 (32.7)	9 (17.0)	14 (23.7)	12 (22.2)	52 (23.9)
Gender						
Male	N (%)	48 (92.3)	47 (88.7)	50 (84.7)	50 (92.6)	195 (89.4)
Female	N (%)	4 (7.7)	6 (11.3)	9 (15.3)	4 (7.4)	23 (10.6)
Race						
White	N (%)	35 (67.3)	37 (69.8)	41 (69.5)	42 (77.8)	155 (71.1)
Black/African American	N (%)	13 (25.0)	13 (24.5)	15 (25.4)	9 (16.7)	50 (22.9)
Asian	N (%)	3 (5.8)	1 (1.9)	2 (3.4)	0	6 (2.8)
Other	N (%)	1 (1.9)	2 (3.8)	1 (1.7)	3 (5.6)	7 (3.2)
Weight (kg)	Mean	45.6	38.9	44.8	42.2	42.9
< 40 kg	N (%)	24 (46.2)	35 (66.0)	33 (55.9)	34 (63.0)	126 (57.8)
≥ 40 kg	N (%)	28 (53.8)	18 (34.0)	26 (44.1)	20 (37.0)	92 (42.2)
Height (cm)	Mean	144.9	136.5	142.3	139.3	140.8
BMI (kg/m <sup>2</sup> )	Mean	20.49	19.91	21.06	20.14	20.41

### Baseline Disease Characteristics

The ABC, CGI-S, and CY-BOCS ratings from the end of baseline are presented in Table 9. Mean baseline ratings were similar between treatment groups.

**Table 9 Baseline Disease Characteristics, Randomized Sample, Study CN138179**

Scale	Placebo N=52	Aripiprazole 5 mg N=53	Aripiprazole 10 mg N=59	Aripiprazole 15 mg N=54	Total N=218
ABC, mean (SD)					
Irritability	28.0 (6.89)	28.6 (7.56)	28.2 (7.36)	28.9 (6.41)	28.4 (7.04)
Hyperactivity	32.7 (11.0)	33.7 (9.99)	34.7 (10.17)	33.2 (8.56)	33.6 (9.93)
Stereotypy	10.7 (6.25)	11.1 (5.70)	11.5 (5.65)	11.6 (4.56)	11.2 (5.4)
Social Withdrawal	18.8 (11.15)	17.2 (9.96)	17.0 (9.17)	18.9 (8.65)	17.9 (9.72)
Inappropriate Speech	6.4 (3.74)	6.0 (3.85)	7.0 (4.10)	6.4 (3.87)	6.5 (3.89)

Scale	Placebo N=52	Aripiprazole 5 mg N=53	Aripiprazole 10 mg N=59	Aripiprazole 15 mg N=4	Total N=218
CGI-Severity, mean (SD)	4.9 (0.76)	5.1 (0.84)	4.9 (0.71)	5.1 (0.77)	5.0 (0.77)
CY-BOCS, mean (SD) Compulsion	13.8 (3.09)	13.7 (4.38)	13.3 (4.58)	13.9 (4.68)	13.7 (4.23)

### Patient Disposition

A total of 368 patients were enrolled in the study. Of these, 218 patients were randomized to receive treatment: 52 in placebo, 53 in aripiprazole 5 mg, 59 in aripiprazole 10 mg, and 54 in aripiprazole 15 mg group. A total of 178 (81.7%) of the 218 randomized patients completed the double-blind phase of the study, 38 (73.1%) in the placebo group, 44 (83.0%) in the 5-mg aripiprazole group, 49 (83.1%) in the 10-mg group, and 47 (87.0%) in the 15-mg group. The most frequent reason for discontinuation in all treatment groups was due to AEs: 4 (7.7%) in placebo, 5 (9.4%) in aripiprazole 5 mg, 8 (13.6%) in aripiprazole 10 mg, and 4 (7.4%) in aripiprazole 15 mg group.

Placebo treatment was associated with higher discontinuation rate (26.9%) and higher rate of discontinuation due to lack of efficacy (5.8%) compared with aripiprazole treated groups (13 to 17%, and 0% respectively).

The disposition of randomized patients is presented in Table 10.

**Table 10 Disposition of Patients, Study CN138179 (Double-Blind Phase), Randomized Sample**

Patient Status	Placebo	Aripiprazole 5 mg	Aripiprazole 10 mg	Aripiprazole 15 mg	Total
Randomized, n	52	53	59	54	218
Completed, n (%)	38 (73.1)	44 (83.0)	49 (83.1)	47 (87.0)	178 (81.7)
Discontinued, n (%)	14 (26.9)	9 (17.0)	10 (16.9)	7 (13.0)	40 (18.3)
Lack of efficacy	3 (5.8)	0	0	0	3 (1.4)
Adverse event	4 (7.7)	5 (9.4)	8 (13.6)	4 (7.4)	21 (9.6)
Subject withdrew consent	2 (3.8)	2 (3.8)	1 (1.7)	0	5 (2.3)
Lost to follow-up	3 (5.8)	1 (1.9)	0	1 (1.9)	5 (2.3)
Poor/non-compliance	1 (1.9)	1 (1.9)	1 (1.7)	1 (1.9)	4 (1.8)
Other	1 (1.9)	0	0	1 (1.9)	2 (0.9)

All randomized patients were included in the Safety Sample except for 2 patients, 1 in the placebo group who no longer met study criteria and 1 in the aripiprazole 5-mg group who withdrew consent to participate. Three patients were not included in the Efficacy Sample (2 in the placebo group: one was lost to follow up and one withdrew consent to participate; and 1 in the aripiprazole 15-mg group: due to elevated potassium level).

### Concomitant Medication Use

The most commonly used CNS concomitant medications during this study for all treatment groups were “other analgesics and antipyretics” (placebo, 17.6%; aripiprazole 5 mg, 23.1%; 10 mg, 20.3%; and 15 mg, 22.2%). One (2.0%) placebo-treated patient and 10 (6.1%) aripiprazole-treated patients (5 mg, 4 [7.7%]; 10 mg, 1 [1.7%]; 15 mg, 5 [9.3%]) took a concomitant medication for potential treatment of EPS. Only a few patients used anxiolytic (3 [5.9%] in placebo, and 1-2 [1.7 to 3.8%] in aripiprazole treatment groups) and hypnotic & sedative (2 [3.9%] in placebo, and 1-2 [1.7 to 3.8%] in aripiprazole treatment group) during the study. It is unlikely that the concomitant medication use during this study had affected the final efficacy outcome.

### Protocol Deviations

Clinical relevant protocol deviations were identified during the study and were summarized in Table 11. No patient was excluded from the analyses because of a relevant protocol deviation.

**Table 11 Protocol Deviations of Clinical Relevance, Study CN138179**

<b>Deviation</b>	<b>Number of Patients N = 218<sup>a</sup></b>
Treated WOCBP patients with missing or positive pregnancy test within 3 Days prior to start of study medication	1
Randomized Patients with exclusionary ABC Irritability Subscale score	2
Randomized patients with missing vital signs at screening or baseline	44
Treated patients given wrong study medication	4
Randomized patients with concomitant prohibited or restricted medications	13
Treated patients with study medication not administered per protocol	16

### Efficacy Findings

#### *Primary Efficacy Endpoint*

The primary endpoint was the mean change from baseline to Week 8 LOCF in the ABC Irritability Subscale score. All 3 doses of aripiprazole demonstrated statistically significant improvement compared with placebo on the primary efficacy endpoint—the mean change from baseline to Week 8 LOCF in the ABC Irritability Subscale score (placebo: -8.4; arip. 5 mg: -12.4, difference = 4.0, p = 0.032; arip. 10 mg: -13.2, difference = -4.8, p = 0.008; arip. 15 mg: -14.4, difference -6.0, p = 0.001) (see



### **iii. Conclusions**

In study CN138179, all 3 doses of aripiprazole at doses of 5, 10 and 15 mg, demonstrated clinically relevant and statistically significant improvement compared with placebo on the primary efficacy endpoint at Week 8 (LOCF), the adjusted mean change from baseline on the ABC Irritability Subscale score.

The statistical reviewer, Steve Bai PhD., reanalyzed the data using LOCF analysis and confirmed the primary efficacy findings. He also performed an analysis on the treatment effect over time based on an MMRM method and found that the treatment effects were consistent with the primary efficacy results.

## **c. Crosscutting Issues**

### **i. Subgroup Analyses**

For the population subset analyses (age, gender, and race) of the ABC Irritability Subscale score, results from both studies were consistently in favor of aripiprazole across all subsets and none of the treatment-by-subgroup interaction terms were statistically significant. An additional analysis using different age groupings (6 to 11 and 12 to 17 years) was conducted and showed no statistically significant interaction.

### **ii. Dose Response**

Study CN138178 is a flexible-dose study. No dose response relationship can be identified from this study. Study CN138179 is a fixed-dose study and consists of 3 aripiprazole treatment arms, 5, 10, and 15 mg. Even though all three aripiprazole doses showed significant efficacy compared with placebo at week 8, no dose-response relationship was found in this study. The higher aripiprazole dose groups (10 and 15 mg) did slightly better than the 5 mg group in reduction of ABC irritability subscale score at week 8 (placebo adjusted mean change: -4.0, -4.8, and -6.0 in arip. 5, 10, and 15 mg respectively). But, clearly the differences were small and there was no dose-response relationship identified.

### **iii. Key Secondary Endpoints**

In CN138178, the mean CGI-Improvement score was the key secondary efficacy measure; in CN138179, it was a secondary efficacy measure but was not considered a key secondary measure.

In CN138178, the treatment difference of the mean CGI-Improvement score achieved statistically significant improvement for aripiprazole compared with placebo at Week 8

(-1.4,  $p < 0.001$ , LOCF). The treatment differences were also statistically significant in favor of aripiprazole for all dose groups in CN138179 (5 mg: -0.7,  $p = 0.003$ ; 10 mg: -0.8,  $p < 0.001$ ; and 15 mg: -0.8,  $p < 0.001$ ). These findings were confirmed by our statistical reviewer.

#### iv. Effect Size

The acute efficacy of aripiprazole in treatment of irritability associated with autistic disorder were demonstrated in two 8 weeks, double-blind, placebo-controlled studies: CN138178, a flexible-dose study (2 to 15 mg) and CN138179, a fixed-dose study (5, 10, and 15 mg).

The only drug that has been approved for the same indication in the USA is risperidone (NDA 20-272/S036). The acute efficacy of risperidone in reducing irritability-like symptomatology in autistic patients aged 5 to 16 was demonstrated in two 8-week, flexible-dose, double-blind, placebo-controlled studies, CAN-23 (n=80) and USA-150/Part I (n=101). The risperidone doses ranging from 0.02 to 0.06 mg/kg in CAN-23, and ranging from 0.25mg to 2.5mg (for weight between 20kg and 45kg) or 0.5mg to 3.5 mg/day (for 45kg and over).

A primary efficacy measure in all 4 studies (2 aripiprazole and 2 risperidone studies) was the ABC Irritability subscale.

The mean changes from baseline to week 8 (LOCF) in the ABC Irritability subscale in the 4 clinical trials (CN138178, CN138179, CAN-23 and USA-150/Part I) are displayed in Table 14. The mean decreases from baseline are also represented as fractions (%) of the baseline values.

**Table 14 Effect Size Comparison between Aripiprazole and Risperidone Clinical Trials**

	Aripiprazole Studies (LOCF)						Risperidone Studies (LOCF)			
	CN138178		CN138179				CAN-23		USA-150/Part I	
	PLA	Arip.	PLA	Arip. 5 mg	Arip. 10 mg	Arip. 15 mg	PLA	Risp.	PLA	Risp.
Baseline	30.8	29.6	26.9	28.3	27.6	28.3	21.6	20.6	25.0	26.1
Week 8	-5.0	-12.9	-8.4	-12.4	-13.2	-14.4	-7.5	-13.5	-3.5	-14.9
% Reduction	-16	-44	-31	-44	-48	-51	-35	-66	-14	-57
Difference from placebo		-7.9		-4.0	-4.8	-6.0		-6.0		-11.4

The effect sizes in aripiprazole studies were comparable with that seen in study CAN-23 and smaller than that obtained from study USA-150/Part I. This comparison is only a rough comparison because the nature of the studies (where, when, testing medications, dose, sample size, study population) was different. It is hard to perform the direct comparison without bias. However, in both aripiprazole trials, the mean decreases in the

Irritability subscale score were  $\geq 44\%$  of the baseline value of the aripiprazole treated groups. Changes of such magnitude are likely to be clinically significant.

#### **v. Long-term Efficacy**

No long-term study for the indication of irritability associated with autistic disorder was conducted by the sponsor. A long-term efficacy and safety study for this indication is required by the division as a phase 4 commitment.

#### **vi. Pediatric Development**

These two aripiprazole studies were conducted in children aged 6 to 17. No more short term pediatric study will be required. A long-term efficacy and safety study for the maintenance treatment indication is requested by the division as a post-marketing commitment.

#### **d. Efficacy Conclusion Regarding the Indication of Irritability Associated with Autism Disorder**

Individual analyses of the 2 placebo-controlled studies in patients with autistic disorder showed that treatment with aripiprazole is efficacious in improving the symptoms of irritability in children and adolescents with autism, as demonstrated by results on the primary endpoint, ABC Irritability Subscale.

In both studies, aripiprazole showed clinically meaningful and statistically significant improvement compared with placebo within 1 to 2 weeks that continued throughout the study to endpoint (Week 8) on the primary efficacy measures.

In both studies, the treatment difference of the mean CGI-Improvement score (a key secondary endpoint of study CN138178) achieved statistically significant improvement for all aripiprazole treated groups compared with placebo at Week 8.

There was no dose-response pattern with respect to efficacy for the primary endpoint.

None of the treatment-by-subgroup interaction terms (age, gender and race) were statistically significant.

## 7 Review of Safety

### 7.1 Methods

#### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

There are two datasets were used in the integrated safety review:

Placebo-controlled Studies in Autistic Disorder: Data from patients in the 2 completed pivotal studies (CN138178, and CN138179) have been pooled for presentation.

All Pediatric Aripiprazole Dataset: Cumulative data on all pediatric patients exposed to aripiprazole in all Phase 2/3 studies includes studies 31-03-238,31-03-239, 31-03-240, 31-03-241, 31-05-243, CN138014 and the 3 autistic disorder studies (CN138178, CN138179, CN138180).

During this sNDA review, a 120-Day Safety Update were submitted on May 21, 2009, which presents a review of the safety of the oral-tablet formulation in the clinical trials database as of the cutoff date of 15-Nov-2008. A summarization of post-marketing safety information, including a review of Periodic Safety Update Reports (PSURs) as of 16-Jul-2008, is also presented.

#### 7.1.2 Categorization of Adverse Events

An AE was defined as any new untoward medical occurrence or worsening of a preexisting medical condition regardless of causal relationship with treatment. An AE could be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational or marketed) product, whether or not considered related to the medicinal (investigational or marketed) product.

A SAE was any untoward medical occurrence at any dose that:

- results in death
- is life-threatening (defined as an event in which the subject or patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a cancer

- is a congenital anomaly/birth defect
- results in the development of drug dependency or drug abuse
- is an important medical event (including pregnancy or overdose)

### **7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence**

Data from patients in the two completed pivotal studies (CN138178, CN138179) have been pooled for presentation because of similarity of study design.

## **7.2 Adequacy of Safety Assessments**

### **7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations**

A total of 362 pediatric patients received aripiprazole in the autistic disorder clinical trial program; 920 pediatric patients received aripiprazole across all Phase 1/2/3 studies. Overall, patient exposure years (PEY) total 517.3, with 170.7 years for patients with autistic disorder. Table 15 presents a summary of the number of patients who received aripiprazole in the safety sample of these studies.

**Table 15 Summary of Patients Who Received Aripiprazole in the Safety Sample**

Pools by Indication and Study Design	Enumeration of Patients by Treatment Group	
	Placebo	Aripiprazole
Autistic Disorder		
8-Week Placebo-Controlled	101	212
Ongoing, Uncontrolled/Open-Label		313
Total Autistic Disorder	101	(163) (a) 362
Schizophrenia		
Short-Term Placebo-Controlled	100	202
Ongoing, Uncontrolled/Open-Label		240
Total Schizophrenia	100	(160) (a) 282
Bipolar Disorder		
Short-Term Placebo-Controlled	97	197
Uncontrolled/Open-Label		98
Total Bipolar Disorder	97	(50) (a) 245
Other Indications		
Conduct Disorder		23
Other		8
Total Other Indications		31
Total Phase 1/2/3 Exposure	298	920

(a) The number of patients also counted under Aripiprazole in the Placebo-Controlled row.

There were 212 patients who received aripiprazole during the randomization phase of the placebo-controlled studies in autistic disorder and 85.4% of these patients received between 50 - 56 days of study drug. There were 52.8% of patients who received overall mean doses of aripiprazole of > 7.5 mg - ≤ 12.5 mg, 41.0% who received > 3.5 mg - ≤ 7.5 mg, and 6.1% who received ≤ 3.5 mg. No patient had an overall mean dose of > 12.5 mg/day during the 8-week placebo-controlled phase.

In the 120-Day Safety Update (SU) submitted on 21 May 2009, the sponsor reported that the extent of exposure of patients in all pediatric disorder patients was similar to that reported in the original submission.

## 7.2.2 Explorations for Dose Response

Study CN138-189 is a fixed-dose study. The safety data from each dose group were analyzed separately. The Cochran-Armitage Exact test was conducted to assess the dose-response relationship of AEs (ie, increased incidence of AEs with increased dose) and was analyzed including and excluding placebo.

### **7.2.3 Special Animal and/or In Vitro Testing**

No special animal and/or In Vitro testing was deemed necessary.

### **7.2.4 Routine Clinical Testing**

Routine clinical testing includes deaths, adverse events (serious AEs and common AEs), safety laboratory tests (hematology, clinical chemistry and urinalysis), vital signs, body weight, ECG and plasma prolactin levels.

### **7.2.5 Metabolic, Clearance, and Interaction Workup**

Atypical antipsychotics as a class are associated with metabolic syndrome. To explore metabolic effects of aripiprazole, mean changes from baseline values and clinically significant changes for blood glucose, lipids, body weight, and BMI over time were studied.

### **7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class**

Atypical antipsychotics are associated with increased prolactin levels, EPS, and metabolic syndrome. Plasma prolactin, glucose, and lipid (cholesterol, triglycerides, LDL and HDL) levels were tested during the study. Body weight, BMI, and EPS were assessed over time during the study.

## **7.3 Major Safety Results**

### **7.3.1 Deaths**

There were no deaths among 362 pediatric patients exposed to aripiprazole in all autistic disorder studies.

### **7.3.2 Nonfatal Serious Adverse Events**

Serious adverse events (SAEs) were reported in 2 (0.9%) aripiprazole-treated patients during the autistic disorder studies: 1 event of presyncope that was mild and considered possibly related to treatment and 1 event of aggression that was severe/very severe and considered not likely related to treatment.

### 7.3.3 Dropouts and/or Discontinuations

A total of 10.4% aripiprazole-treated and 7.9% placebo-treated patients discontinued from the placebo-controlled studies in autistic disorder (see Table 16). The most frequently reported reason for discontinuation in the aripiprazole group was sedation (3.3%); in the placebo group it was mania (2.0%).

**Table 16 Summary of Discontinuation Due to Adverse Events, CN138178 & CN138179, Safety Sample**

System Organ Class/ Preferred Term (b)	Number (%) of Patients (a)	
	Placebo	Aripiprazole
# Pts in Safety Sample	101	212
# Male Pts in Safety Sample	91	188
# Female Pts in Safety Sample	10	24
Any AE Leading to Discontinuation	8 ( 7.9)	22 (10.4)
Nervous System Disorders	4 ( 4.0)	14 ( 6.6)
Sedation	0	7 ( 3.3)
Drooling	0	4 ( 1.9)
Tremor	0	4 ( 1.9)
Akathisia	1 ( 1.0)	2 ( 0.9)
Extrapyramidal Disorder	0	3 ( 1.4)
Psychomotor Hyperactivity	1 ( 1.0)	1 ( 0.5)
Convulsion	1 ( 1.0)	0
Dyskinesia	0	1 ( 0.5)
Hyperkinesia	1 ( 1.0)	0
Lethargy	0	1 ( 0.5)
Presyncope	0	1 ( 0.5)
Psychiatric Disorders	4 ( 4.0)	5 ( 2.4)
Aggression	1 ( 1.0)	1 ( 0.5)
Mania	2 ( 2.0)	0
Agitation	0	1 ( 0.5)
Flat Affect	0	1 ( 0.5)
Impulsive Behaviour	1 ( 1.0)	0
Insomnia	1 ( 1.0)	0
Intentional Self-Injury	0	1 ( 0.5)
Intermittent Explosive Disorder	0	1 ( 0.5)
Negativism	1 ( 1.0)	0
Social Avoidant Behaviour	0	1 ( 0.5)
General Disorders And Administration	1 ( 1.0)	3 ( 1.4)
Site Conditions		
Irritability	1 ( 1.0)	1 ( 0.5)
Fatigue	0	1 ( 0.5)
Gait Disturbance	0	1 ( 0.5)
Gastrointestinal Disorders	0	3 ( 1.4)
Vomiting	0	3 ( 1.4)

System Organ Class/ Preferred Term (b)	Number (%) of Patients (a)	
	Placebo	Aripiprazole
Eye Disorders	0	2 ( 0.9)
Conjunctivitis	0	1 ( 0.5)
Eye Rolling	0	1 ( 0.5)
Investigations	1 ( 1.0)	1 ( 0.5)
Alanine Aminotransferase Increased	1 ( 1.0)	0
Weight Increased	0	1 ( 0.5)
Metabolism And Nutrition Disorders	0	2 ( 0.9)
Decreased Appetite	0	1 ( 0.5)
Increased Appetite	0	1 ( 0.5)
Cardiac Disorders	0	1 ( 0.5)
Tachycardia	0	1 ( 0.5)
Injury, Poisoning And Procedural Complications	1 ( 1.0)	0
Laceration	1 ( 1.0)	0
Musculoskeletal And Connective Tissue Disorders	0	1 ( 0.5)
Musculoskeletal Stiffness	0	1 ( 0.5)
Renal And Urinary Disorders	0	1 ( 0.5)
Urinary Incontinence	0	1 ( 0.5)
Vascular Disorders	0	1 ( 0.5)
Hypertension	0	1 ( 0.5)

In All Pediatric Aripiprazole Dataset, the overall incidence of treatment-emergent AEs that led to discontinuation of study therapy was similar across all indications.

### 7.3.4 Significant Adverse Events

#### Neuroleptic Malignant Syndrome (NMS)

A comprehensive search of the AE database for all Phase 1/2/3 pediatric studies was completed to identify aripiprazole-treated patients who had NMS reported as an AE. Of the 920 pediatric patients exposed to aripiprazole, 1 pediatric schizophrenia patient had an AE of NMS. This case was previously reported in the schizophrenia/bipolar mania combined submission. No autistic disorder patients reported NMS.

#### Seizures

A comprehensive search of the AE database for all Phase 1/2/3 pediatric studies was conducted to identify patients with a seizure-related AE using the following terms: seizure, convulsion, grand mal, petit mal, epilepsy, fits, electroencephalogram, EEG,

and lobe. There were no seizure-related AEs in aripiprazole-treated patients in the placebo controlled studies in autistic disorder.

### Suicide-Related Events

AEs related to suicidality were identified in the AE database based on the following search criteria:

- Any AE text term or MedDRA preferred term (PT) with the text string 'suici'
- Any AE with a MedDRA PT of 1 of the following: completed suicide, intentional overdose, intentional self-injury, multiple drug overdose intentional, poisoning deliberate, self injurious behavior, self mutilation, suicide attempt, intentional misuse, depression suicidal, self-injurious ideation, suicidal ideation

The reported events were grouped into 3 categories for presentation purposes, and were defined as follows:

- Completed Suicide: completed suicide
- Suicide Attempt: intentional overdose, intentional self-injury, multiple drug overdose intentional, poisoning deliberate, self injurious behaviour, self mutilation, suicide attempt, intentional misuse
- Suicidal Ideation: depression suicidal; self-injurious ideation; suicidal ideation

In the placebo-controlled studies in autistic disorder, the incidence of suicide-related AEs was 0.5% in the aripiprazole group and 4.0% in the placebo group (Table 17). No aripiprazole-treated patient completed suicide during these studies.

**Table 17 Incidence of Treatment-Emergent Suicide-Related AEs, CN138178 & CN138179, Safety Sample**

System Organ Class/ Preferred Term (b)	Number (%) of Patients (a)	
	Placebo N=101	Aripiprazole N=212
Any Suicide-Related AE	4 ( 4.0)	1 ( 0.5)
Suicide Attempt	3 ( 3.0)	1 ( 0.5)
Self Injurious Behaviour	3 ( 3.0)	0
Intentional Self-Injury	0	1 ( 0.5)
Suicidal Ideation	1 ( 1.0)	0
Self-Injurious Ideation	1 ( 1.0)	0

In All Pediatric Aripiprazole Dataset, the overall incidence of suicide-related AEs was similar across the indications.

Extrapyramidal Symptoms (EPS)

*Incidence of Treatment-Emergent EPS-Related AEs*

Overall, 20.8% of aripiprazole-treated and 9.9% of placebo-treated patients reported EPS-related AEs in the placebo-controlled studies in autistic disorder (see Table 18). The incidence of non-akathisia EPS-related AEs was 17.9% in aripiprazole-treated patients and 2.0% in placebo-treated patients, and the incidence of akathisia events was 3.3% in the aripiprazole group and 8.9% in the placebo group. The most frequently reported events in aripiprazole-treated patients were tremor (9.9% aripiprazole; 0% placebo) and extrapyramidal disorder (6.1% aripiprazole; 0% placebo).

**Table 18 Incidence of Treatment-Emergent EPS-Related AEs, CN138178 & CN138179, Safety Sample**

EPS Category/ Preferred Term (b)	Number (%) of Patients (a)	
	Placebo N=101	Aripiprazole N=212
Any EPS-Related AE	10 ( 9.9)	44 (20.8)
Non-Akathisia Events	2 ( 2.0)	38 (17.9)
Akathisia Events	9 ( 8.9)	7 ( 3.3)
Parkinsonism Events	0	35 (16.5)
Tremor	0	21 ( 9.9)
Extrapyramidal Disorder	0	13 ( 6.1)
Hypokinesia	0	2 ( 0.9)
Bradykinesia	0	1 ( 0.5)
Cogwheel Rigidity	0	1 ( 0.5)
Akathisia Events	9 ( 8.9)	7 ( 3.3)
Psychomotor Hyperactivity	4 ( 4.0)	4 ( 1.9)
Akathisia	4 ( 4.0)	3 ( 1.4)
Hyperkinesia	1 ( 1.0)	0
Dyskinetic Events	1 ( 1.0)	3 ( 1.4)
Dyskinesia	1 ( 1.0)	3 ( 1.4)
Dystonic Events	1 ( 1.0)	1 ( 0.5)
Muscle Rigidity	0	1 ( 0.5)
Muscle Spasms	1 ( 1.0)	0

In the fixed-dose study (CN138179), the events of tremor and extrapyramidal disorder (patient reported 2 or more EPS AEs simultaneously) showed an increased incidence with increasing aripiprazole dose level (see Table 19).

**Table 19 Incidence of Treatment-Emergent EPS-Related AEs, CN138179, Safety Sample**

EPS Category/ Preferred Term (b)	Number (%) of Patients (a)			
	Placebo N=51	Aripiprazole		
		5 mg N=52	10 mg N=59	15 mg N=54
Any EPS-Related AE	6 (11.8)	12 (23.1)	13 (22.0)	12 (22.2)
Parkinsonism Events	0	6 (11.5)	11 (18.6)	12 (22.2)
Tremor	0	4 (7.7)	7 (11.9)	6 (11.1)
Extrapyramidal Disorder	0	2 (3.8)	4 (6.8)	6 (11.1)
Bradykinesia	0	0	0	1 (1.9)
Cogwheel Rigidity	0	0	0	1 (1.9)
Hypokinesia	0	1 (1.9)	0	0
Akathisia Events	5 (9.8)	4 (7.7)	2 (3.4)	0
Akathisia	3 (5.9)	1 (1.9)	2 (3.4)	0
Psychomotor Hyperactivity	2 (3.9)	3 (5.8)	0	0
Dyskinetic Events	1 (2.0)	2 (3.8)	1 (1.7)	0
Dyskinesia	1 (2.0)	2 (3.8)	1 (1.7)	0

Discontinuation due to EPS-related AEs occurred at a similar rate in the aripiprazole group (4.2%) and in the placebo group (3.0%). The most common EPS-related AE that led to discontinuation of study therapy in the aripiprazole group was tremor.

### *EPS Scales*

Results of mean change from baseline to endpoint and highest score in EPS scales are presented in Table 20.

There were statistically significant differences between the groups on the mean change from baseline to endpoint (LOCF) in the SAS Total Score. There was no change from baseline in the aripiprazole group while the placebo group showed improvement.

There was also a statistically significant difference between the groups on the mean change from baseline to endpoint (LOCF) in the AIMS Total Score. The aripiprazole group showed improvement and there was no change in the placebo group.

There were no differences at endpoint between the treatment groups in the Barnes Akathisia Clinical Global Assessment score.

**Table 20 Adjusted Mean Change from Baseline to Endpoint and Highest Score of SAS, AIMS Total Score and Barnes Akathisia Global Clinical Assessment (LOCF), CN138178 & CN138179, Safety Sample**

EPS Scale (a)	Placebo	Aripiprazole	Aripiprazole vs Placebo p-value (b)
SAS Total Score	N=92	N=203	
Mean Baseline (SE)	11.2 (0.24)	10.9 (0.15)	
Change from Baseline at Endpoint (SE)	-0.4 (0.20)	0.1 (0.15)	0.030
Change from Baseline at Highest Score (SE)	0.4 (0.27)	1.2 (0.21)	0.012
AIMS Total Score	N=98	N=209	
Mean Baseline (SE)	0.7 (0.23)	0.7 (0.15)	
Change from Baseline at Endpoint (SE)	-0.0 (0.11)	-0.4 (0.09)	0.005
Change from Baseline at Highest Score (SE)	0.6 (0.18)	0.2 (0.14)	0.096
Barnes Akathisia	N=95	N=209	
Mean Baseline (SE)	0.3 (0.07)	0.1 (0.03)	
Change from Baseline at Endpoint (SE)	0.1 (0.06)	-0.0 (0.04)	0.106
Change from Baseline at Highest Score (SE)	0.3 (0.07)	0.2 (0.05)	0.055

## Metabolic and Glucose Assessment

### *Weight Gain*

The AE of weight gain associated with aripiprazole treatment seemed more prominent in this submission. At the end of the 8-week treatment, aripiprazole treated patients gained average 1.6 kg compared with 0.4 kg in placebo treated patient and 26.3% of aripiprazole treated patients compared with 7.1% of placebo-treated patients gained  $\geq 7\%$  of their body weight from baseline. There was a wider age range (6-17years old) in this autistic program. Normal growth/development should be taken consideration while analyzing the weight data.

### Placebo-Controlled Studies

On the adjusted mean change from baseline to endpoint (LOCF) in body weight, there were statistically significant differences between the treatment groups in the placebo-controlled autistic disorder studies. The adjusted mean change in body weight was higher in the aripiprazole group than the placebo group (1.6 kg vs. 0.4 kg, respectively,  $p < 0.001$ ), and the adjusted mean change from baseline to endpoint (LOCF) in body weight Z-score was higher in the aripiprazole group compared with the placebo group (0.12 standard deviations vs. -0.01 standard deviations, respectively,  $p < 0.001$ ).

On potentially clinically relevant weight gain (an increase of at least  $\geq 7\%$  from baseline), there was a statistically significantly greater number of aripiprazole-treated patients (26.3%) than placebo-treated patients (7.1%) who demonstrated weight gain at endpoint (LOCF). However, there was no statistically significant difference ( $p = 0.849$ ) between aripiprazole and placebo groups in the percentage of patients with clinically

relevant weight, as defined by Z-scores in the 95th percentile or higher. One aripiprazole-treated patient discontinued from the studies because of weight increase.

In order to further explore the weight gain associated with aripiprazole treatment in these studies and to identify potential risk factors, the statistical reviewer, Steven Bai PhD, had conducted additional analyses on the weight data requested from the sponsor during this review cycle. The following are some of his findings.

Aripiprazole and placebo treated patients had average baseline weight Z-score of 0.762 and 0.928 respectively, which correspond to the 77.7th and the 82.3th percentiles of their respective populations. This suggests that patients in these two studies were heavier than age-matched general population at the baseline, and the patients in placebo arm were heavier compared with aripiprazole group. Aripiprazole patients increased their mean body weight Z-score by 0.105 standard deviations at the end of 8 weeks, which corresponds to a ~3% upward shift (77.7% to 80.7%) in the population body weight percentiles. The placebo group, on the other hand, reduced by 0.015 standard deviations in Z-score, which corresponds to a 0.4% decrease (82.3% to 81.9%) of the population body weight percentiles.

Dr. Bai also performed additional analyses on the baseline body weight Z-score, age and gender. Please refer to his review for detailed analysis result. He found that with aripiprazole treatment the heavier (baseline z-score > 75%) and younger (6 to 12 years old) subjects tended to gain more weight ( $p < 0.0001$  in both occasions). It is also noted that younger patients had a larger mean baseline weight Z-score (heavier) compared with the other age group (0.835 versus 0.74, corresponding to the 79.8th and 77th percentiles). The pooled data seems to suggest that baseline weight Z-score and age group more or less contributed to the treatment differences in change from baseline at the endpoint in body weight Z-score.

#### All Pediatric Database

The incidence of potentially clinically relevant weight increase ( $\geq 7\%$  increases from baseline) in aripiprazole-treated pediatric patients by treatment indication is listed in Table 21. More aripiprazole-treated patients (62%) in autistic disorder studies gained clinically significant weight ( $\geq 7\%$  baseline weight) compared with patients in other indication studies (43% in bipolar studies and 37% in schizophrenia studies). The autistic program included younger children: 79% (249/316) of the patients were 12 or younger. It is possible that younger children are more vulnerable to aripiprazole induced weight gain. Dr. Bai's analyses on weight data obtained from the controlled dataset showed that heavier (baseline Z-score > 75% of population body weight percentiles) and younger (6 to 12 years old) children tended to gain more weight during the controlled, autistic studies. The rates of clinically relevant weight gain over time in autistic disorder studies are presented in Table 22. Table 23 summarizes the baseline

body weight, the weight change over time, the corresponding z-scores, and the weight change in percent of population body weight percentiles over time.

Interpretation of these findings is complicated by lack of a placebo control group and the fact that they do not take into account normal weight gain during development. However, Z-score analysis, which does take into account weight gain during development, demonstrated that there was an increase in weight relative to normal growth up to the period of 3-6 months, but then remained stable (6-9 months) or decreased (> 9 months).

**Table 21 Incidence of Weight Gain  $\geq$ 7% from Baseline by Indication, Overall, Safety Sample**

Variable	Number (%) of Aripiprazole Patients			
	Autistic Disorder N=361	Bipolar Disorder N=239	Schizophrenia N=276	All Aripiprazole (a) N=906
Weight (b)				
Weight Increase	224 (62.0)	103 (43.1)	103 (37.3)	447 (49.3)

**Table 22 Incidence of Weight Gain  $\geq$ 7% from Baseline in Autistic Studies by Time, Overall, Safety Sample**

Variable	Number (%) of Aripiprazole Patients (a)			
	$\leq$ 3 months N=361	3-6 months N=238	6-9 months N=165	>9 months N=85
Weight (b)				
Weight Increase	133 (36.8)	153 (64.3)	108 (65.5)	46 (54.1)

**Table 23 Summary of weight change over time in autistic disorder program, overall, safety sample**

	Study Months			
	$\leq$ 3 months Mean, n=354	3-6 months Mean, n=220	6-9 months Mean, n=141	> 9 months Mean, n=61
Body Weight (kg):				
Baseline	43.22	43.99	45.7	48.58
$\Delta$ from Baseline	1.32	4.45	6.12	7.31
Body Weight Z-Score:				
Baseline	0.727	0.727	0.772	0.796
$\Delta$ from Baseline	0.102	0.259	0.253	0.207
$\Delta$ of population body weight percentile (increase)	3%	7%	7%	6%

### *Lipids and Glucose Assessment*

The incidence of treatment emergent metabolic and glucose laboratory measurements of potential clinical relevance (total cholesterol, HDL, LDL, triglycerides, and glucose) during the placebo-controlled studies in autistic disorder was similar between the treatment groups. The limited sample size and study design preclude meaningful interpretation of the results.

There were no hyperglycemia-related AEs reported during the placebo-controlled studies in autistic disorder.

### Prolactin

There was a statistically significant mean decrease in prolactin at endpoint in the aripiprazole group (-5.41 ng/mL) compared with the placebo group (1.21 ng/mL) (Table 24). There was no apparent dose-response relationship between prolactin and aripiprazole dose (Table 25).

**Table 24 Analysis of Prolactin Levels, CN138178 & CN138179, Safety Sample**

	Prolactin Level (a)		P-value
	Placebo	Aripiprazole	
Sample Size (b)	74	170	
Mean Baseline	6.84	7.96	0.214
Mean Change at Endpoint	1.21	-5.41	<0.001

**Table 25 Analysis of Prolactin Levels by Dose, CN138179, Safety Sample**

	Prolactin Level			
	Placebo	Aripiprazole		
		5 mg	10 mg	15 mg
Sample Size (a)	36	43	50	41
Mean Baseline	6.92	7.19	6.54	6.67
Mean Change at Endpoint	0.79	-5.73	-4.99	-5.68

### **7.3.5 Submission Specific Primary Safety Concerns**

No submission specific primary safety concerns were identified.

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

The criteria currently used to determine common AEs are those AEs that occurred at an incidence of  $\geq 5\%$  (including numbers that equaled 5% after rounding) and twice the rate of placebo. For the placebo-controlled studies in autistic disorder, events of sedation, fatigue, somnolence, tremor, drooling, pyrexia, extrapyramidal disorder, decreased appetite, and salivary hypersecretion, vomiting, and lethargy met these criteria. Table 26 summarizes the overall incidence of treatment-emergent adverse events (TEAEs) occurred  $\geq 2\%$  in aripiprazole treated group in placebo-controlled dataset.

**Table 26 Incidence of Treatment-Emergent AEs Occurred  $\geq 2\%$  in Aripiprazole Group, CN138178 & CN138179, Safety Sample**

System Organ Class/ Preferred Term (b)	Placebo	Aripiprazole
# Pts in Safety Sample	101	212
# Male Pts in Safety Sample	91	188
# Female Pts in Safety Sample	10	24
Any AE	75 (74.3)	189 (89.2)
Nervous System Disorders	27 (26.7)	114 (53.8)
Headache	10 (9.9)	16 (7.5)
Somnolence	4 (4.0)	22 (10.4)
Extrapyramidal Disorder	0	13 (6.1)
Sedation	4 (4.0)	44 (20.8)
Akathisia	4 (4.0)	3 (1.4)
Tremor	0	21 (9.9)
Dizziness	0	0
Drooling	0	19 (9.0)
Lethargy	0	10 (4.7)
Dystonia	0	0
Hypersomnia	0	5 (2.4)
Gastrointestinal Disorders	21 (20.8)	71 (33.5)
Vomiting	7 (6.9)	29 (13.7)
Nausea	3 (3.0)	8 (3.8)
Diarrhoea	9 (8.9)	16 (7.5)
Abdominal Pain Upper	2 (2.0)	8 (3.8)
Salivary Hypersecretion	1 (1.0)	12 (5.7)
Constipation	4 (4.0)	11 (5.2)
Stomach Discomfort	0	1 (0.5)
Dry Mouth	0	3 (1.4)
Dyspepsia	0	1 (0.5)

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System Organ Class/ Preferred Term (b)	Placebo	Aripiprazole
# Pts in Safety Sample	101	212
# Male Pts in Safety Sample	91	188
# Female Pts in Safety Sample	10	24
Psychiatric Disorders	26 (25.7)	44 (20.8)
Insomnia	11 (10.9)	11 (5.2)
Aggression	7 (6.9)	6 (2.8)
Agitation	2 (2.0)	5 (2.4)
Anxiety	0	2 (0.9)
Restlessness	3 (3.0)	5 (2.4)
Schizophrenia	0	0
General Disorders And Administration Site Conditions	7 (6.9)	59 (27.8)
Fatigue	2 (2.0)	35 (16.5)
Pyrexia	1 (1.0)	19 (9.0)
Asthenia	0	0
Thirst	1 (1.0)	5 (2.4)
Infections And Infestations	18 (17.8)	43 (20.3)
Nasopharyngitis	5 (5.0)	18 (8.5)
Upper Respiratory Tract Infection	5 (5.0)	6 (2.8)
Gastroenteritis Viral	2 (2.0)	6 (2.8)
Respiratory, Thoracic And Mediastinal Disorders	16 (15.8)	46 (21.7)
Cough	5 (5.0)	13 (6.1)
Nasal Congestion	2 (2.0)	9 (4.2)
Rhinorrhoea	2 (2.0)	8 (3.8)
Epistaxis	0	7 (3.3)
Metabolism And Nutrition Disorders	10 (9.9)	41 (19.3)
Increased Appetite	7 (6.9)	27 (12.7)
Decreased Appetite	2 (2.0)	14 (6.6)
Musculoskeletal And Connective Tissue Disorders	5 (5.0)	11 (5.2)
Arthralgia	1 (1.0)	3 (1.4)
Back Pain	0	0
Musculoskeletal Stiffness	0	5 (2.4)
Investigations	4 (4.0)	12 (5.7)
Weight Increased	3 (3.0)	8 (3.8)
Skin And Subcutaneous Tissue Disorders	4 (4.0)	12 (5.7)
Rash	2 (2.0)	5 (2.4)
Eye Disorders	5 (5.0)	3 (1.4)
Vision Blurred	0	0
Renal And Urinary Disorders	5 (5.0)	14 (6.6)
Enuresis	5 (5.0)	7 (3.3)
Reproductive System And Breast Disorders	0	3 (1.4)
Dysmenorrhoea*	0	0

The incidence of TEAEs that occurred in  $\geq 5\%$  in different aripiprazole dosing groups and placebo group in study CN138-179 is presented in Table 27. Sedation, tremor, drooling, extrapyramidal disorder, salivary hypersecretion, fatigue and pyrexia are reported in higher frequency in higher aripiprazole dose groups and showed a dose response trend, but they are not statistically significant when placebo was included in the analysis. Fatigue is the only AE which showed a statistically significant dose-response relationship.

**Table 27 Incidence of Treatment-Emergent Adverse Events that Occurred in  $\geq 5\%$  of Patients by Treatment Group, CN138-179, Safety Sample**

System Organ Class Preferred Term (b)	Number (%) of Patients (a)			
	Placebo	Aripiprazole 5 mg	Aripiprazole 10 mg	Aripiprazole 15 mg
# Pts in Safety Sample	51	52	59	54
# Male Pts in Safety Sample	47	46	50	50
# Female Pts in Safety Sample	4	6	9	4
Any Adverse Event	37 (72.5)	46 (88.5)	53 (89.8)	46 (85.2)
Nervous System Disorders	13 (25.5)	24 (46.2)	39 (66.1)	28 (51.9)
Sedation	3 ( 5.9)	9 (17.3)	17 (28.8)	13 (24.1)
Tremor	0	4 ( 7.7)	7 (11.9)	6 (11.1)
Somnolence	2 ( 3.9)	4 ( 7.7)	5 ( 8.5)	5 ( 9.3)
Drooling	0	2 ( 3.8)	8 (13.6)	5 ( 9.3)
Headache	2 ( 3.9)	3 ( 5.8)	5 ( 8.5)	5 ( 9.3)
Extrapyramidal Disorder	0	2 ( 3.8)	4 ( 6.8)	6 (11.1)
Lethargy	0	4 ( 7.7)	3 ( 5.1)	3 ( 5.6)
Akathisia	3 ( 5.9)	1 ( 1.9)	2 ( 3.4)	0
Hypersomnia	0	3 ( 5.8)	0	2 ( 3.7)
Psychomotor Hyperactivity	2 ( 3.9)	3 ( 5.8)	0	0
Gastrointestinal Disorders	9 (17.6)	11 (21.2)	22 (37.3)	24 (44.4)
Vomiting	4 ( 7.8)	5 ( 9.6)	12 (20.3)	5 ( 9.3)
Diarrhoea	4 ( 7.8)	2 ( 3.8)	5 ( 8.5)	5 ( 9.3)
Constipation	3 ( 5.9)	2 ( 3.8)	6 (10.2)	3 ( 5.6)
Salivary Hypersecretion	1 ( 2.0)	1 ( 1.9)	4 ( 6.8)	6 (11.1)
Nausea	1 ( 2.0)	1 ( 1.9)	3 ( 5.1)	4 ( 7.4)
Abdominal Pain Upper	1 ( 2.0)	2 ( 3.8)	1 ( 1.7)	4 ( 7.4)
Psychiatric Disorders	13 (25.5)	12 (23.1)	13 (22.0)	9 (16.7)
Insomnia	6 (11.8)	1 ( 1.9)	5 ( 8.5)	2 ( 3.7)
Aggression	3 ( 5.9)	2 ( 3.8)	3 ( 5.1)	0
General Disorders And Administration Site Conditions	1 ( 2.0)	9 (17.3)	20 (33.9)	16 (29.6)
Fatigue	0	2 ( 3.8)	13 (22.0)	10 (18.5)
Pyrexia	0	3 ( 5.8)	7 (11.9)	5 ( 9.3)
Thirst	1 ( 2.0)	3 ( 5.8)	1 ( 1.7)	1 ( 1.9)

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System Organ Class Preferred Term (b)	Number (%) of Patients (a)			
	Placebo	Aripiprazole 5 mg	Aripiprazole 10 mg	Aripiprazole 15 mg
Respiratory, Thoracic And Mediastinal Disorders	7 (13.7)	13 (25.0)	16 (27.1)	9 (16.7)
Cough	2 ( 3.9)	8 (15.4)	4 ( 6.8)	0
Rhinorrhoea	1 ( 2.0)	2 ( 3.8)	5 ( 8.5)	1 ( 1.9)
Nasal Congestion	1 ( 2.0)	1 ( 1.9)	1 ( 1.7)	4 ( 7.4)
Pharyngolaryngeal Pain	3 ( 5.9)	1 ( 1.9)	1 ( 1.7)	1 ( 1.9)
Epistaxis	0	0	4 ( 6.8)	1 ( 1.9)
Infections And Infestations	6 (11.8)	13 (25.0)	9 (15.3)	13 (24.1)
Nasopharyngitis	2 ( 3.9)	6 (11.5)	5 ( 8.5)	5 ( 9.3)
Gastroenteritis Viral	0	1 ( 1.9)	3 ( 5.1)	1 ( 1.9)
Upper Respiratory Tract Infection	0	2 ( 3.8)	0	3 ( 5.6)
Metabolism And Nutrition Disorders	4 ( 7.8)	14 (26.9)	8 (13.6)	11 (20.4)
Increased Appetite	2 ( 3.9)	10 (19.2)	3 ( 5.1)	7 (13.0)
Decreased Appetite	1 ( 2.0)	5 ( 9.6)	5 ( 8.5)	3 ( 5.6)
Skin And Subcutaneous Tissue Disorders	3 ( 5.9)	3 ( 5.8)	4 ( 6.8)	3 ( 5.6)
Rash	1 ( 2.0)	0	3 ( 5.1)	1 ( 1.9)
Investigations	1 ( 2.0)	4 ( 7.7)	3 ( 5.1)	3 ( 5.6)
Weight Increased	1 ( 2.0)	4 ( 7.7)	1 ( 1.7)	2 ( 3.7)
Renal And Urinary Disorders	1 ( 2.0)	2 ( 3.8)	1 ( 1.7)	7 (13.0)
Enuresis	1 ( 2.0)	0	1 ( 1.7)	3 ( 5.6)
Immune System Disorders	5 ( 9.8)	1 ( 1.9)	0	1 ( 1.9)
Seasonal Allergy	4 ( 7.8)	0	0	1 ( 1.9)

#### **7.4.2 Laboratory Findings**

In the placebo-controlled studies in autistic disorder, the incidences of treatment-emergent serum chemistry laboratory abnormalities of potential clinical relevance and serum electrolyte measurements were similar between treatment groups. No patient had elevated ALT, AST, or total bilirubin. No aripiprazole-treated patient discontinued from the studies because of a laboratory abnormality. There were no clinically meaningful serum chemistry findings by age, gender, or race.

#### **7.4.3 Vital Signs**

The incidences of potentially clinically relevant vital sign measurements for the placebo-controlled studies in autistic disorder were generally similar between treatment groups. One aripiprazole-treated patient discontinued from the study because of hypertension. There were no clinically meaningful vital sign findings by age, gender, or race.

#### **7.4.4 Electrocardiograms (ECGs)**

In the placebo-controlled studies in autistic disorder, the incidence of potentially clinically relevant ECG abnormalities was low for aripiprazole-treated patients and comparable to that of placebo-treated patients except for the measurement of sinus tachycardia and the non-specific category of other abnormalities. The incidence of sinus tachycardia was higher in aripiprazole-treated patients (2.6%) than placebo-treated patients (0%), and 1 aripiprazole-treated patient discontinued from the study because of tachycardia.

The data from all aripiprazole Phase 1/2/3 studies are presented as the mean change from baseline to study endpoint and mean change from baseline to maximum on-treatment QTcE (fractional exponent correction method). No clinically meaningful differences were observed between treatment groups in the mean change from baseline to endpoint and at maximum reading in QTcE measurements. No aripiprazole-treated patient demonstrated a QTcE greater than 500 msec or > 60 msec change in QTcE interval. There were no clinically meaningful differences between the treatment groups by gender, age, or race.

#### **7.4.5 Special Safety Studies/Clinical Trials**

No special safety studies were conducted for this indication.

#### **7.4.6 Immunogenicity**

No immunogenicity study was deemed necessary.

## **7.5 Other Safety Explorations**

### **7.5.1 Dose Dependency for Adverse Events**

The Cochran-Armitage Exact test was conducted by the sponsor to assess the dose-response relationship of AEs (ie, increased incidence of AEs with increased dose) and was analyzed including and excluding placebo. When placebo was included in the analysis, the AEs of sedation, tremor, drooling, extrapyramidal disorder, salivary hypersecretion, fatigue, and pyrexia showed a statistically significant ( $p < 0.05$ ) dose-response relationship. When placebo was excluded from the analysis, only the AE of fatigue showed a statistically significant dose-response relationship.

### **7.5.2 Time Dependency for Adverse Events**

The time dependency for adverse events was not studied in this submission.

### **7.5.3 Drug-Demographic Interactions**

The overall incidences of treatment-emergent AEs were similar across age groups for aripiprazole-treated and placebo-treated patients. There was a statistically significant difference between the age groups for the event of salivary hypersecretion (ages 6 - 12: 6.6% aripiprazole; 0% placebo; ages 13 - 17: 2.2% aripiprazole; 4.5% placebo), indicating that this event was more prominent in younger children than older children with autistic disorder. Tremor occurred more frequent in children aged 6 to 12 with aripiprazole treatment (11.4%, vs. 0% in PLA) compared with in children aged 13 to 17 with aripiprazole treatment (4.4%, vs. 0% in PLA).

There was no clinically meaningful difference in the AE profile (aripiprazole versus placebo) between males and females. However, the limited number of females precluded meaningful interpretation of AEs relative to gender across groups.

In general, there was no difference in the AE profile among racial groups. However, the limited number of patients in racial groups other than white and black precluded meaningful interpretation of AEs relative to race across all groups.

### **7.5.4 Drug-Disease Interactions**

No drug-disease interactions were studied in this submission.

### **7.5.5 Drug-Drug Interactions**

Aripiprazole is a marketed drug in the USA for many years. Drug-drug interaction profile had been well established and has been addressed in current approved aripiprazole

labeling. No drug-drug interaction studies were deemed necessary in the aripiprazole autistic disorder clinical program.

## **7.6 Additional Safety Evaluations**

### **7.6.1 Human Carcinogenicity**

No human carcinogenicity study was deemed necessary.

### **7.6.2 Human Reproduction and Pregnancy Data**

No pregnancies were reported in this autistic disorder program.

### **7.6.3 Pediatrics and Assessment of Effects on Growth**

This submission included two 8-week, short-term studies. Significant weight gain associated with aripiprazole treatment was observed in both studies. Please refer to section 7.3.5 *Submission Specific Primary Safety Concerns* for more discussion regarding the weight gain issue. Height change was not assessed during these two trials.

### **7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound**

A comprehensive review of aripiprazole-treated patients participating in autistic disorder studies was conducted to identify cases of overdose. No cases of overdose were identified in aripiprazole-treated patients in autistic disorder studies.

A comprehensive review of aripiprazole-treated patients participating in autistic disorder studies was conducted to identify AEs that might indicate possible abuse of aripiprazole. No cases of drug abuse were identified in the pediatric autistic disorder population.

No studies were conducted in patients with autistic disorder to assess withdrawal and rebound.

## **7.7 Additional Submissions / Safety Issues**

A 120-Day Safety Update (SU) was submitted on May 21, 2009 presented a review of the safety of the oral-tablet formulation based on data available in the clinical trials database as of the cutoff date of 15-Nov-2008.

Newly-reported data since the cutoff date for the autistic disorder clinical summary of safety (CSS) were reviewed for deaths, SAEs, and discontinuations due to AEs, and are

presented in this SU. The cut-off date for the autistic disorder CSS was 1-Jun-2008 for all ongoing studies.

The extent of exposure of patients in all pediatric autistic disorder patients for this SU was similar to that reported in the autistic disorder CSS. A total of 367 pediatric autistic disorder patients have been treated with aripiprazole in Phase 3 studies. Of these, 243 (66.2%) patients were treated with aripiprazole for 180 days or longer.

Data in this SU on the aripiprazole tablet formulation in pediatric patients were reviewed for discontinuations due to AE, SAEs, and deaths. The safety and tolerability of aripiprazole as demonstrated in this SU (data cutoff 15-Nov-2008) indicate a safety profile consistent with that reported in other pediatric indications. Results are consistent with what has been seen throughout the development and marketing of oral-tablet aripiprazole. No new safety concerns were identified.

## 8 Postmarket Experience

Aripiprazole was first approved for the treatment of schizophrenia in adults on 17-Jul-2002 (International Birth Date) in Mexico and subsequently in the United States on 15-Nov-2002 and the European Union on 4-Jun-2004. Aripiprazole was approved for use in adolescent schizophrenia in the United States on 29-Oct-2007 and the application is currently under review in the European Union. In addition, aripiprazole was approved for acute manic or mixed episodes associated with Bipolar I Disorder in adults in the United States on 29-Sep-2004, and in pediatric patients on 27-Feb-2008. It is also approved for acute mania in adults in the EU, Switzerland, Turkey, Brazil, Indonesia, Korea, Mexico, Venezuela, Chile, Colombia, Egypt, Hong Kong, Peru, and Russia.

An estimate of the number of treated patients was derived from sales figures received from IMS for the period from 1-Oct-2002 to 31-Mar-2008 inclusive. Based on the information available to Otsuka/BMS, (b) (4) milligrams (mg) were sold during the period referenced above. The total number of patients exposed during the period referenced above is estimated to be (b) (4).

Review of the aripiprazole worldwide AE data received from spontaneous postmarketing reports and from clinical trials, as presented in the PSURs, PADERs, indicated an overall benefit risk profile similar to and consistent with the previously established clinical trial experience as described in the Company Core Safety Information (CCSI) and in the existing USPI for Abilify.

## 9 Appendices

### 9.1 Literature Review/References

A worldwide literature search for published articles pertaining to the safety and efficacy of aripiprazole was conducted. The literature search timeframe includes published articles from June 1, 2007 through a cut-off date of June 30, 2008.

This literature search encompassed databases searched from 01June2007 through 30June2008. Search terms included the keywords: aripiprazole, abilitat, abilify, opc()14597 or opc14597, opc()31 or opc31.

Databases searched via Dialog from 31January 2008 through 30June 2008 included the following:

- MEDLINE(R) 1990-2008/Aug 04
- Biosis Previews(R) 1993-2008/Aug W1
- EMBASE 1993-2008/Aug 05
- EMBASE Alert 2008/Aug 06
- Derwent Drug File 1983-2008/Jun W4
- SciSearch(R) Cited Ref Sci 1990-2008/Jul W4
- CA SEARCH(R) 1967-2008/UD=14905
- ToxFile 1965-2008/Jul W4
- Int.Pharm.Abs 1970-2008/May B2
- Adis Clinical Trials Insight 1990-2008/Jul W4

Databases searched via STN prior to 31January2008 included the following:

- MEDLINE
- BIOSIS/Biological Abstracts
- EMBASE/EMBASE ALERTS
- DRUGU/Derwent Drug File
- SCISEARCH/Science Citation Index
- CAPLUS/Chemical Abstracts
- TOXCENTER
- LIFESCI/Life Sciences Collection
- IPA/International Pharmaceutical Abstracts
- ADISCTI: Adis Clinical Trials Insight.

Following the review, it has been determined that the literature contains no findings that would adversely affect conclusions about the safety and efficacy of aripiprazole contained in supplemental submission to NDA 21-436.

## 9.2 Labeling Recommendations

The following are the sponsor proposed changes and the reviewer's recommendations. Changes are shown as ~~strikethroughs~~ for deletion and underline for addition.

In section 6.1 Overall Adverse Reactions Profile/Weight Gain, the sponsor proposed following addition:



In section 14.4, the sponsor proposed following addition:

### *14.4 Irritability Associated with Autistic Disorder*

#### *Pediatric Patients*

*The efficacy of ABILIFY (aripiprazole) in the treatment of irritability associated with Autistic Disorder was established in two 8-week, placebo-controlled trials in pediatric patients (6 to 17 years of age) who met the DSM-IV criteria for Autistic Disorder and demonstrated behaviors such as tantrums, aggression, self-injurious behavior, or a combination of these problems. Over 75% of these subjects were under 13 years of age.*

*Efficacy was evaluated using two assessment scales: the Aberrant Behavior Checklist (ABC) and the Clinical Global Impression-Improvement (CGI-I) scale. The primary outcome measure in both trials was the change from baseline to endpoint in the Irritability subscale of the ABC (ABC-I). The ABC-I subscale measured the emotional and behavioral symptoms of irritability in Autistic Disorder, including aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods. The results of these trials are as follows:*

- 1. In one of the 8-week, placebo-controlled trials, children and adolescents with Autistic Disorder (n=98), aged 6 to 17 years, received daily doses of placebo or ABILIFY 2 mg/day to 15 mg/day. ABILIFY, starting at 2 mg/day and increasing up to 15 mg/d base on clinical response and tolerability, significantly improved scores on the ABC-I subscale and on the CGI-I scale compared with placebo. The mean daily dose of aripiprazole at the end of 8 weeks was 8.6 mg/day.*

*2. In the other 8-week, placebo-controlled trial in children and adolescents with Autistic Disorder (n=218), aged 6 to 17 years, three fixed doses of ABILIFY (5 mg/day, 10 mg/day, or 15 mg/day) were compared to placebo. ABILIFY dosing started at 2 mg/day and was increased to 5 mg/day after one week. After a second week, it was increased to 10 mg/day for patients in the 10 mg and 15 mg dose arms, and after a third week, it was increased to 15 mg/day in the 15 mg/day treatment arm. All three doses of ABILIFY significantly improved scores on the ABC-I subscale compared with placebo.*

The reviewer has reviewed all other proposed clinical related labeling changes. The changes are acceptable.

### **9.3 Advisory Committee Meeting**

No advisory committee meeting is planned for this submission.

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-21436

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SUPPL-27

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OTSUKA  
PHARMACEUTICA  
L CO LTD

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ABILIFY (ARIPRAZOLE)  
10/15/20/30MG

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/s/  
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JING ZHANG  
10/30/2009

## ADDENDUM

### Review and Evaluation of Clinical Data NDA #021436/027

<b>Sponsor:</b>	Otsuka Pharmaceutical Co, Ltd
<b>Drug:</b>	Aropiprazole
<b>Proposed Indication:</b>	Irritability Associated with Autistic Disorder
<b>Material Submitted:</b>	Original sNDA submission
<b>Correspondence Date:</b>	21 January 2009
<b>Date Received:</b>	22 January 2009
<b>Related NDA:</b>	

This sNDA was submitted on 21 January 2009 and my original clinical review was completed on 30 October 2009 and has been filed into DARRTS. Due to technical problems that occurred while the Word file (my review) was converted to a PDF file, part of the information (track-changes) in section of 9.2 Labeling Recommendations was lost in DARRTS. This addendum includes the original review of section 9.2 Labeling Recommendations.

### 9.2 Labeling Recommendations

The following are the sponsor proposed changes and the reviewer's recommendations. Changes are shown as ~~strikethroughs~~ for deletion and underline for addition.

(b) (4)

The reviewer has reviewed all other proposed clinical related labeling changes.  
The rest proposed changes are acceptable.

Jing Zhang, M.D., Ph.D.  
November 1, 2009

cc: NDA 21436/027  
HFD-130 (Div. File)  
HFD-130 /T Laughren  
/M Mathis  
/R Temple  
/J Zhang  
/K Ansah

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-21436

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SUPPL-27

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OTSUKA  
PHARMACEUTICA  
L CO LTD

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ABILIFY (ARIPRAZOLE)  
10/15/20/30MG

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JING ZHANG  
11/01/2009

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 21-436/S027**

**CHEMISTRY REVIEW(S)**

**Division of Post Approval Marketing Evaluation IV  
Chemist Review of Supplement**

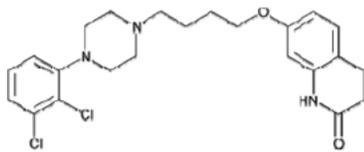
1. Division of Post Approval Marketing IV
2. NDA Number: 21436
3. Supplement Numbers: SCE-027
- Letter Date: January 21, 2009/August 19, 2009
- Stamp Date: January 21, 2009/ August 19, 2009
4. Amendments/Reports/Dates:
5. Received by Chemist: August 25, 2009

6. Applicant Name and Address: Bristol Meyers Squibb Otsuka  
 PO Box 5100 2400 Research Blvd  
 Wallingord, CT 06492 Rockville, MD 20850

7. Name of the Drug: Abilify®  
 8. Nonproprietary name: Aripiprazole

9. Chemical Structure/ Chemical Name:

Chemical Name: (b) (4) 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydro-  
 Molecular formula: C<sub>23</sub>H<sub>27</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>2</sub>  
 MW: 448.39  
 CAS: 129722-12-9  
 Chemical Structure:



10. Dosage Form: Tablets
11. Potency: 2mg, 5mg an 10mg, 15mg, 20mg and 30mg
12. Pharmacological Category: Schizophrenia and bipolar mania
13. How Dispensed: XXX (RX) \_\_\_\_\_ (OTC)
14. Records and Reports current XXX (yes) \_\_\_\_\_ (No)
15. Related IND/NDA/DMF: \_\_\_\_\_ (yes) XXX (No)

16. **Comments/Conclusions:** This PA supplement provides for a new indication for the treatment of irritability associated with autistic disorder in pediatric patients, aged 6 to 17 years of age. Development of this drug product is under a collaborative agreement between Otsuka and BMS. The current submission is in response to an approval letter by the Agency (July 19, 2009) wherein further labeling additions to the Warnings and Precautions Section, were requested. There is no new CMC information provided in this submission or that of January 19, 2009. However, the Sponsor has requested a categorical exclusion from the preparation of an environmental assessment, under 21 CFR 25.31 (a), based on an estimate that the concentration of the active moiety in the environment will remain at less than 1 ppb, regardless of the potential increase in use, due to the additional indication.

**17. Recommendations: Recommend Approval of this Supplement**

18.. Reviewer Name

\_\_\_\_\_  
 Julia C. Pinto, Ph.D., Chemist

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

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NDA-21436

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SUPPL-27

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OTSUKA  
PHARMACEUTICA  
L CO LTD

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ABILIFY (ARIPRAZOLE)  
10/15/20/30MG

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/s/  
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JULIA C PINTO  
09/23/2009

JAMES D VIDRA  
09/23/2009

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 21-436/S027**

**STATISTICAL REVIEW(S)**



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

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

**NDA #/Serial #:** 21-436 /S\_27

**DRUG NAME:** Aripiprazole (Abilify)

**INDICATION:** Treatment of Irritability Associated with Autistic Disorder

**APPLICANT:** Otsuka

**DATE OF RECEIPT:** 01/21/2009

**REVIEW PRIORITY:** Standard

**BIOMETRICS DIVISION:** Division of Biometrics I

**STATISTICAL REVIEWER:** Steve Bai, Ph.D. (HFD-710)

**CONCURRENT REVIEWER:** Peiling Yang, Ph.D. (HFD-710)  
Kooros Mahjoob, Ph.D. (HFD-710)

**MEDICAL DIVISION:** Division of Psychiatry Products (HFD-130)

**CLINICAL REVIEWER:** Zhang Jing, M.D. (HFD-130)

**PROJECT MANAGER:** Ansah Kofi, Pharm. D. (HFD-130)

**KEY WORDS:** MMRM, Autistic Disorder

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## **1 EXECUTIVE SUMMARY**

### **1.1 Conclusions and Recommendations**

The sponsor's Aripiprazole autistic disorder program consisted of 2 placebo-controlled studies of identical design except that fixed dosing was used for one (CN138179) and flexible dosing for the other (CN138178).

In the flexible-dose study (CN138178), Aripiprazole demonstrated statistically significant efficacy relative to placebo in treating irritability in children and adolescents (ages 6-17 years) with a diagnosis of autistic disorder, as assessed by the mean change from baseline on the ABC Irritability Subscale at Week 8 of the treatment phase. Aripiprazole also produced statistically significant improvements over placebo on the key secondary efficacy measure, the change in CGI-I score at Week 8.

The fixed-dose study CN138179 evaluated target Aripiprazole doses of 5, 10 and 15 mg/day. All 3 dose groups demonstrated statistically significantly greater efficacy than placebo in treating irritability in children and adolescents (ages 6-17 years) with a diagnosis of autistic disorder, as measured by the mean change from baseline to Week 8 on the ABC Irritability Subscale.

### **1.2 Brief Overview of Clinical Studies**

The Aripiprazole autistic disorder program consisted of 2 placebo-controlled studies of identical design except that fixed dosing was used for one (CN1381794) and flexible dosing for the other (CN1381785).

In CN138178, Aripiprazole was flexibly dosed at 2- 15 mg/day. All patients randomized to treatment with Aripiprazole started the study at the 2-mg dose for Week 1; the dose could be increased to 5 mg at Week 2, to 10 mg at Week 3, and to 15 mg at Week 4. No dose increases could occur after Week 6. If the dose was intolerable, the dose could be decreased at any time. There were 164 patients enrolled at 19 study centers in the United States from June 15, 2006 through February 18, 2008.

In CN138179, patients were randomized to either placebo or a target dose 5, 10, or 15 mg/day Aripiprazole. All Aripiprazole-treated patients started the study at 2 mg for Week 1. The 5-mg Aripiprazole group reached the randomized dose at Week 2, the 10-mg Aripiprazole group at Week 3, and the 15-mg Aripiprazole group at Week 4. If the dose was intolerable, patients were discontinued from the study. There were 368 patients enrolled at 33 study centers in the United States from June 15, 2006 through March 19, 2008.

The primary efficacy endpoint of both studies was the mean change from baseline to endpoint (Week 8, last observation carried forward [LOCF]) in the ABC Irritability Subscale score.

### 1.3 Statistical Issues and Findings

Both studies were positive on the primary endpoint. In study CN138178, the efficacy of Aripiprazole flexible doses (2 to 15 mg/day) versus placebo in the adjusted (by the ANCOVA model) mean change from baseline on the ABC Irritability Subscale at the endpoint visit (Week 8 LOCF) was demonstrated. In addition, Aripiprazole flexible dose also demonstrated statistically significant improvement compared with placebo on the key secondary efficacy endpoint, the clinician rated CGI-I score at the endpoint visit (Week 8 LOCF). In study CN138179, the efficacy of Aripiprazole at 5-, 10-, and 15-mg/day doses versus placebo in the adjusted mean change from baseline on the ABC Irritability Subscale starting at the endpoint visit (Week 8 LOCF) was demonstrated with three statistically significant p-values.

## 2 INTRODUCTION

### 2.1 Overview

This review provides a statistical evaluation of Aripiprazole as a treatment of irritability associated with autistic disorder in children and adolescents of ages 6 to 17 years.

Autistic disorder is a neurodevelopmental disorder characterized by abnormalities in social interaction, communication, and the presence of restricted and repetitive behaviors. Although not strictly part of the diagnostic criteria, there are many secondary behavioral features that are commonly associated with autism. These include irritability and tantrums, attention and/or hyperactivity disorders, self-injury, odd responses to sensory stimuli, lack of fear or excessive fearfulness, and many others. Many of these can profoundly impair functioning and cause substantial individual and family burden. Reducing symptom burden as much as possible is a commonly accepted therapeutic goal but few studies are available to guide clinicians on how to treat problematic symptoms.

ABILIFY (Aripiprazole) is approved for the treatment of schizophrenia and acute manic or mixed episodes associated with bipolar I disorder in adults in the United States (US, the European Union (EU), and several other countries. ABILIFY is also approved in the US as adjunctive treatment in adult patients with major depressive disorder. In pediatric patients, ABILIFY is approved in the US for the treatment of schizophrenia in adolescents (ages 13-17) and in children and adolescents (ages 10-17) with bipolar I disorder. Although Risperdal is the only drug approved for treating pediatric patients with irritability associated with autistic disorder, alternative treatment options would be beneficial in this setting where there remains a high unmet medical need.

This Aripiprazole autistic disorder program consisted of 2 placebo-controlled studies of identical design except that fixed dosing was used for one and flexible dosing for the other. Sponsor attempted to use these two studies to demonstrate Aripiprazole can be used as an alternative treatment option for treating irritability in children and adolescents (ages 6 - 17 years) with a diagnosis of autistic disorder.

## 2.2 Data Sources

The sponsor's submitted data are stored in the following directory of the CDER's electronic document room: [\\fdswa150\NONECTD\N21436\S\\_027\2009-01-21\crt\datasets](\\fdswa150\NONECTD\N21436\S_027\2009-01-21\crt\datasets)

## 3 STATISTICAL EVALUATION

### 3.1 Evaluation of Efficacy

The following description is based on the sponsor's clinical study report. Any discrepancy between the study report and study protocol will be discussed in the section of statistical reviewer's comments.

#### 3.1.1 STUDY CN138178

The objective of this study was to compare the efficacy of flexibly dosed Aripiprazole with that of placebo in reducing serious behavioral problems, specifically irritability, agitation, and self-injurious behavior, in children and adolescents with a diagnosis of Autistic Disorder, as measured by change from baseline to the endpoint visit on the Irritability Subscale of the Aberrant Behavior Checklist (ABC). In addition, as a key secondary objective, this study was also interested to compare the efficacy of Aripiprazole with placebo as measured by the clinician-rated Clinical Global Impression of Improvement (CGI-I).

##### 3.1.1.1 Study Design

This was a double-blind, randomized, placebo-controlled, parallel-group, multicenter 8-week study designed to assess the efficacy, safety, and tolerability of Aripiprazole flexibly dosed in children and adolescents with a diagnosis of autistic disorder with serious behavioral problems characterized by irritability, agitation, and self-injurious behavior. This study consisted a screening phase of up to 42 days followed by an 8-week treatment phase.

Patients were randomized to treatment with either Aripiprazole (2 to 15 mg/day) or placebo in a 1:1 ratio. All patients randomized to Aripiprazole started the study at the 2-mg dose for week 1; the dose could be increased to 5 mg at week 2, to 10 mg at week 3, and to 15 mg at week 4. No dose increase could occur after week 6. If the dose was intolerable, the dose could be decreased at any time. The mean daily dose of Aripiprazole for all patients in the safety sample at endpoint was 8.5 mg/day, see Figure 1. Patients who completed the 8-week treatment were eligible for an open-label long term study. There were 164 patients enrolled at 19 study centers in the United States from June 15, 2006 through February 18, 2008.

**Figure 1** Number and Percentages of Patients Receiving Study Medication and Mean and Range of Mean Daily Double-Blind Dose

Days	Placebo Mean Daily Dose per Week (mg/day) (b)			Aripiprazole Mean Daily Dose per Week (mg/day)				
	N (%)	Mean	Min	Max	N (%)	Mean	Min	Max
Day 1 - 7	50 (100.0)	2.1	2	3	47 (100.0)	2.1	1	3
Day 8 - 14	50 (100.0)	4.4	2	9	45 (95.7)	4.0	2	6
Day 15 - 21	46 (92.0)	7.8	1	15	42 (89.4)	6.2	0	11
Day 22 - 28	42 (84.0)	10.7	2	15	42 (89.4)	7.5	0	15
Day 29 - 35	40 (80.0)	11.9	2	15	41 (87.2)	9.1	0	15
Day 36 - 42	38 (76.0)	11.9	2	15	40 (85.1)	9.0	2	15
Day 43 - 49	38 (76.0)	12.5	2	15	39 (83.0)	8.6	2	15
Day 50 - 56	36 (72.0)	12.8	2	15	39 (83.0)	8.9	2	15
Day >56	14 (28.0)	13.6	5	15	13 (27.7)	10.0	5	15
Endpoint (a)	50 (100.0)	11.4	2	15	47 (100.0)	8.5	1	15

[Source: Sponsor's CSR Table 6.1]

### 3.1.1.2 Efficacy Measures

The primary efficacy measure was the mean change from baseline to endpoint (Week 8) in the ABC Irritability Subscale score. The key secondary efficacy outcome measure was the mean CGI-I score.

The key secondary efficacy outcome measure was the mean CGI-I score at endpoint (week 8 LOCF).

Other secondary efficacy outcome measures will include the following:

- Mean change from baseline to Weeks 1, 2, 3, 4, 5, and 6 (LOCF and OC), as well as Week 8 (OC) in the ABC Irritability Subscale score
- Mean CGI-I score at Weeks 1, 2, 3, 4, 5 and 6 (LOCF and OC), as well as at Week 8 (OC)
- Mean change from baseline to Weeks 1, 2, 3, 4, 5, 6 and 8 (LOCF and OC) in the following ABC Subscales: Social Withdrawal, Stereotypy, Hyperactivity, and Inappropriate Speech
- Response rate at Weeks 1, 2, 3, 4, 5, 6 and 8 (LOCF and OC) defined as  $\geq 25\%$  reduction from baseline in the ABC Irritability Subscale score AND a CGI-I score of 1 or 2
- Mean change from baseline to Week 8 in the CY-BOCS (LOCF and OC)
- Mean change from baseline to Week 8 in the CGI-S (LOCF and OC)

### 3.1.1.3 Statistical Analysis Plan

The hypothesis of this study is to demonstrate that Aripiprazole flexibly dosed (2-15 mg/day) is more effective than placebo in decreasing serious behavioral problems in children and adolescents with a diagnosis of Autistic Disorder, as measured by the Irritability Subscale of the ABC. The primary analysis will occur at the end of the study after all patients have completed the study. No interim analyses are planned.

It is expected that 100 patients will have to be randomized to obtain 90 evaluable patients (45 per treatment group). This sample size will yield 93% power to differentiate between placebo and the Aripiprazole treatment group when the true difference in the mean changes from baseline in the ABC Irritability Subscale score is 7.0. This assumes a standard deviation of 9.42 and a two sided test at the 0.05 level of significance.

For the purpose of analysis, four different study cohorts have been defined: Enrolled Sample, Randomized Sample, Safety Sample, and Efficacy Sample. The Safety Sample comprises all patients in the Randomized Sample who take at least one dose of study medication during the double-blind Treatment Phase, as identified on the dosing record. The efficacy sample comprises all patients who are in the safety sample and have at least one post-randomization efficacy evaluation and corresponding baseline value.

Furthermore, two different datasets have been defined: LOCF and OC dataset. The LOCF data set includes data recorded at a given time point or, if no observation is recorded at that time point, data carried forward from the previous time point with available data. Baseline data will not be carried forward or averaged with the on treatment data to impute missing values for the LOCF data set. The LOCF data set was the primary data set.

For continuous measurements, such as the ABC Irritability Subscale score, data were evaluated by ANCOVA with treatment, baseline body weight (two categories:  $\geq 40$  kg and  $< 40$  kg), study center as main effects and baseline score as a covariate for the LOCF data set. Categorical measures such as response will be analyzed with the Cochran-Mantel Haenszel (CMH) procedure. For the analysis of the key secondary efficacy endpoint, a hierarchical testing procedure was used in order to protect the overall experiment-wise type I error rate at 0.05. CGI-I would be tested only if the primary efficacy endpoint was statistically significant.

### 3.1.1.4 Patient Disposition, Demographic and Baseline Characteristics

A total of 164 subjects enrolled into the study. Of these, 98 subjects were randomized to receive treatment: 51 patients to the placebo and 47 patients to Aripiprazole. The disposition of these 98 patients is listed in Table 1.

**Table 1 Reasons for Discontinuation**

	Treatment	
	Aripiprazole (N=47) n (%)	Placebo (N=51) n (%)
Completed study	39 (83.0)	36 (70.6)
Terminated due to:		
Adverse event	5 (10.6)	3 (5.9)
Lost to follow up	1 (2.1)	4 (7.8)
Lack of efficacy	1 (2.1)	6 (11.8)
Subject withdrew consent	1 (2.1)	2 (3.9)

[Source: Reviewer's results and Sponsor's Table 5.1 of CSR]

**Demographic characteristics for the Randomized Sample are presented by randomized group in**

Table 2. The mean age of the randomized patients was 9.3 years (range 6 - 17 years). Patients were predominantly male (87.8%) and white (74.5%).

**Table 2 Demographic Characteristics**

Parameter	Category	Statistic	Treatment	
			Placebo	Aripiprazole
Age (years)		Mean (sd)	8.8 (2.57)	9.7 (3.20)
		Median	8.0	9.0
		Min - Max	6-17	6 – 17
Gender	Male	n (%)	44 (86.3)	42 (89.4)
	Female	n (%)	7 (13.7)	5 (10.6)
Race	White	n (%)	41 (80.4)	32 (68.1)
	Black	n (%)	7 (13.7)	11 (23.4)
	Asian	n (%)	0 (0.00)	2 (4.3)
	Other	n (%)	3 (5.9)	2 (4.2)

[Source: Sponsor’s Table 5.3.1 of CSR]

The ABC, CGI-S, and CY-BOCS ratings from the end of baseline are presented in Table 3. Mean baseline rates were similar between treatment groups.

**Table 3 End of Baseline Ratings for Randomized Sample**

Scale		Placebo (N=51)	Aripiprazole (N=47)	Total (N=98)
ABC (Irritability)	N	51	47	98
	Mean	30.2	29.6	29.9
	SD	6.52	6.37	6.42
	Median	30.0	30.0	30.0
	(Min, Max)	(19, 44)	(18, 45)	(18, 45)
ABC (Hyperactivity)	N	51	47	98
	Mean	35.3	34.0	34.7
	SD	8.86	8.64	8.73
	Median	36.0	35.0	36.0
	(Min, Max)	(9, 48)	(14, 48)	(9, 48)
ABC (Stereotypy)	N	51	47	98
	Mean	11.2	11.8	11.5
	SD	5.79	6.13	5.93
	Median	10.0	12.0	11.5
	(Min, Max)	(1, 21)	(0, 21)	(0, 21)
ABC (Social Withdrawal)	N	51	47	98
	Mean	18.8	19.9	19.3
	SD	9.62	11.26	10.40
	Median	20.0	20.0	20.0
	(Min, Max)	(0, 41)	(0, 48)	(0, 48)
ABC (Inappropriate Speech)	N	51	47	98
	Mean	6.8	6.9	6.8
	SD	3.98	3.78	3.87
	Median	8.0	8.0	8.0
	(Min, Max)	(0, 12)	(0, 12)	(0, 12)
Scale		Placebo (N=51)	Aripiprazole (N=47)	Total (N=98)
CGI-Severity	N	51	47	98
	Mean	4.9	4.9	4.9
	SD	0.63	0.71	0.67
	Median	5.0	5.0	5.0
	(Min, Max)	(4, 6)	(4, 6)	(4, 6)
CY-BOCS (Compulsion)	N	51	47	98
	Mean	14.2	12.9	13.6
	SD	3.39	4.94	4.24
	Median	15.0	14.0	14.5
	(Min, Max)	(4, 20)	(0, 20)	(0, 20)

[Source: sponsor’s table 5.3.2 of CSR]

### 3.1.1.5 Sponsor's Key Efficacy Results

The primary endpoint was the mean change from baseline to Week 8 LOCF in the ABC Irritability Subscale score. There was a statistically significant difference between the treatment groups in favor of Aripiprazole in the adjusted mean change from baseline to Week 8 in ABC Irritability Subscale score, see Table 4.

**Table 4 Adjusted Mean Change from Baseline in ABC Irritability Subscale Score**

Statistics	Placebo	Aripiprazole
N	49	46
Mean Baseline (SD)	30.3 (6.6)	29.5 (6.3)
Mean change from Baseline (SE)	-5.0 (1.4)	-12.9 (1.4)
Difference from Placebo	-7.9	
95% CI	(-11.7, -4.1)	
p-value	<.0001	

[Source: Reviewer's results]

### 3.1.1.6 Sponsor's Other Efficacy Results

As a sensitivity analysis, the results in Table 4 were repeated for the OC data set. The results corroborated with the primary findings, and Aripiprazole showed a statistically significantly improvement over placebo, see Table 5.

**Table 5 Sensitivity Analysis: Change from Baseline to Week 8 in the ABC Score**

	Placebo	Aripiprazole
Sample Size at Week 8	34	38
Mean change from Baseline (SE)	-5.2 (1.5)	-14.5 (1.4)
Difference from Placebo	-9.2	
95% CI	(-13.3, -5.2)	
p-value	<.0001	

[Source: Reviewer's results]

For the key secondary efficacy endpoint, the adjusted mean CGI-I score, the difference between the treatment groups in the adjusted mean at Week 8 LOCF was statistically significant in favor of Aripiprazole, see Table 6.

**Table 6 Adjusted Mean CGI-Improvement Score, LOCF Data set**

Statistics	Placebo	Aripiprazole
N	49	46
Mean (SE)	3.6 (.18)	2.2 (.18)
Treatment difference	-1.4	
95% CI	(-1.9, -1.0)	
p-value	<.0001	

[Source: Reviewer's results]

The other secondary endpoints listed in section 3.1.1.2 were also analyzed by the sponsor, but none was pre-specified as key secondary endpoints and no multiple testing procedures was

applied to control the overall study wise Type I error rate. This review only included their means and standard errors as exploratory findings, see Table 7 and Table 8.

**Table 7 Mean Change from Baseline in ABC Irritability Subscale Score, LOCF and OC Data Sets, by Each Visit Week**

Visit	LOCF			
	Placebo		Aripiprazole	
	N	Mean (SE)	N	Mean (SE)
Week 1	46	-2.7 (1.02)	45	-5.5 (1.01)
Week 2	49	-3.6 (1.13)	46	-8.5 (1.13)
Week 3	49	-4.6 (1.18)	46	-10.4 (1.19)
Week 4	49	-6.6 (1.23)	46	-11.8 (1.24)
Week 5	49	-5.7 (1.35)	46	-12.0 (1.36)
Week 6	49	-6.2 (1.43)	46	-13.2 (1.44)
Visit	OC Set			
	Placebo		Aripiprazole	
	N	Mean (SE)	N	Mean (SE)
Week 1	46	-2.5 (0.93)	45	-5.1 (0.92)
Week 2	46	-3.4 (1.01)	42	-8.8 (1.04)
Week 3	43	-4.5 (1.10)	40	-10.8 (1.12)
Week 4	39	-6.0 (1.19)	40	-12.0 (1.16)
Week 5	39	-5.8 (1.30)	39	-12.9 (1.31)
Week 6	38	-7.0 (1.47)	38	-14.6 (1.46)
Week 8	34	-5.2 (1.49)	38	-14.5 (1.41)

[Source: Reviewer's results]

**Table 8 Adjusted Mean CGI-Improvement Score, LOCF and OC Data Sets**

Visit	LOCF Set			
	Placebo		Aripiprazole	
	N	Mean (SE)	N	Mean (SE)
Week 1	46	3.9 (0.14)	45	3.2 (0.13)
Week 2	49	3.6 (0.15)	46	2.8 (0.16)
Week 3	49	3.5 (0.15)	46	2.7 (0.15)
Week 4	49	3.5 (0.18)	46	2.4 (0.18)
Week 5	49	3.6 (0.17)	46	2.4 (0.18)
Week 6	49	3.5 (0.18)	46	2.3 (0.18)
Visit	OC Set			
	Placebo		Aripiprazole	
	N	Mean (SE)	N	Mean (SE)
Week 1	46	4.0 (0.12)	45	3.2 (0.12)
Week 2	46	3.6 (0.13)	43	2.8 (0.14)
Week 3	43	3.4 (0.12)	40	2.7 (0.12)
Week 4	39	3.4 (0.16)	40	2.3 (0.15)

Week 5	39	3.4 (0.16)	39	2.4 (0.17)
Week 6	38	3.3 (0.17)	38	2.2 (0.17)
Week 8	34	3.4 (0.17)	38	2.2 (0.16)

[Source: Reviewer's results]

Aripiprazole also showed numerical improvement over placebo in most of the other ABC subscale scores. Table 9 displayed the mean changes from baseline to Week 8 LOCF for four of those subscale scores.

**Table 9 Mean Change (SE) from Baseline in Other ABC Scores (LOCF)**

	Placebo	Aripiprazole
Hyperactivity	-2.8 (1.5)	-12.7 (1.52)
Stereotype	-2.0 (0.62)	-4.8 (0.63)
Social Withdraw	-6.2 (1.1)	-7.9 (1.2)
Inappropriate Speech	-0.4 (0.4)	-2.5 (0.40)

[Source: Reviewer's results]

Furthermore, Aripiprazole also performed numerically better than placebo in a response rate, which is defined as a reduction  $\geq 25\%$  in ABC Irritability Subscale score compared to baseline and a score of 1 or 2 in the CGI-scale. The response rates are 14.3% vs. 52.2% for placebo and Aripiprazole, respectively.

Finally, the differences between treatment groups in the mean change from baseline to Week 8 LOCF in the CY-BOCS and CGI-S scores were also numerically in favor of Aripiprazole, see Table 10.

**Table 10 Mean Change (SE) from Baseline in CY-BOCS and CGI-S scores**

	Placebo	Aripiprazole
CY-BOCS	-0.8 (0.52)	-3.8 (0.50)
CGI-S	-0.4 (0.15)	-1.2 (0.14)

[Source: Reviewer's results]

### 3.1.1.7 Reviewer's Results and Comments

This reviewer confirms the findings based on the primary efficacy variable as presented in Table 4. Aripiprazole demonstrated statistically significant improvement compared with placebo on the adjusted mean change from baseline on the ABC Irritability Subscale at Week the endpoint visit (Week 8 LOCF).

Furthermore, the findings based on the key secondary efficacy variable were also confirmed as presented in Table 6. Aripiprazole demonstrated statistically significant improvement compared with placebo on the clinician rated CGI-I score at the endpoint visit (Week 8 LOCF).

This reviewer performed an analysis on the treatment effect over time based on an MMRM analysis. The treatment effects appeared to be consistent with the primary efficacy results, see Table 11.

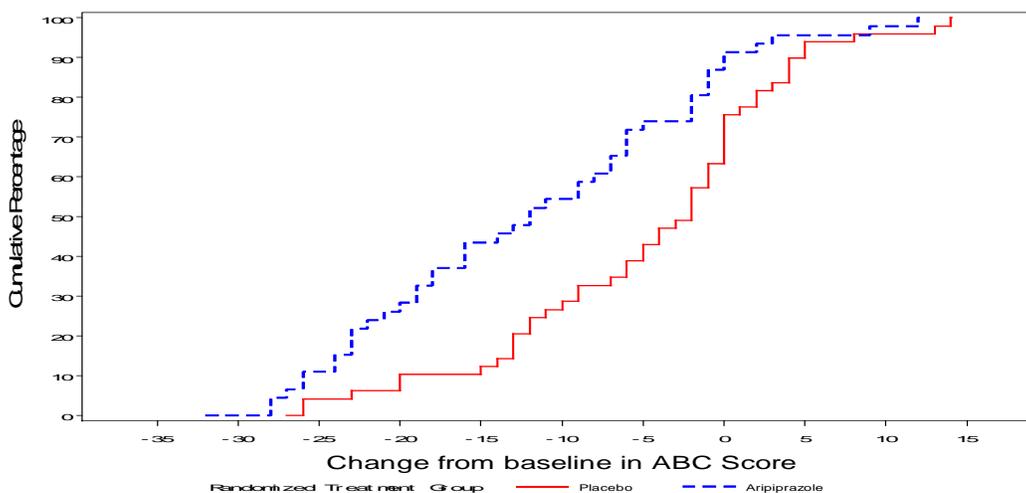
**Table 11** Change from Baseline in ABC Score (MMRM) over Weeks in the ITT sample

Visit	Placebo		Aripiprazole		Aripiprazole-Pbo	
	N	Mean	N	Mean	LS Mean	P-value*
Week 1	49	-2.6	45	-5.4	-2.2	0.08
Week 2	47	-3.4	42	-8.7	-1.9	0.18
Week 3	42	-4.6	41	-10.8	-4.0	0.01
Week 4	39	-5.8	41	-12.1	-3.7	0.04
Week 5	38	-6.1	40	-13.1	-4.9	0.02
Week 6	38	-6.5	40	-13.8	-4.9	0.02
Week 8	34	-5.2	38	-14.5	-7.3	0.0009

[Source: Reviewer’s results]

\*p-values are not adjusted for multiplicity

**Figure 2** Cumulative Distribution Function of the Primary Endpoint by Treatment



[Source: Reviewer’s results]

Figure 2 displays the cumulative probability of these ABC Irritability Subscale score changes from baseline at Week 8 which were plotted across the range of observed values. The vertical axis indicates the proportion of patients whose score changes from baseline were less than or equal to a given number of score change (horizontal axis). For example, 50% of patients in the Aripiprazole group had reduced the score by up to approximately 12 and 50% of patients in the Placebo group had reduced the score only by up to approximately 2. The plots suggested a separation between Aripiprazole and placebo. The cumulative distribution function of Aripiprazole is entirely above of the distribution function of placebo, which is also consistent with the findings in Table 4. The raw means of each treatment group were generated from the LOCF data set, and were used to construct the curves in the Figure 2.

In summary, this study demonstrated the efficacy of Aripiprazole over placebo on the change from baseline to Week 8 in the ABC Irritability Subscale score. In addition, the improvement on the key secondary endpoint, the CGI-I scale, was statistically significantly greater for Aripiprazole versus placebo by the end of the treatment period (Week 8).

### 3.1.2 STUDY CN138179

The objective of this study was to compare the efficacy of Aripiprazole 5 mg, 10 mg, or 15 mg/day with placebo in reducing serious behavioral problems, specifically irritability, agitation, and self-injurious behavior, in children and adolescents with a diagnosis of autistic disorder, as measured by change from baseline to the endpoint visit on the Irritability Subscale of the Aberrant Behavior Checklist (ABC).

In addition, this study also has the following four efficacy secondary objectives:

- To compare the efficacy of Aripiprazole with placebo as measured by the clinician-rated Clinical Global Impression<sup>6</sup> of Improvement (CGI-I)
- To compare the efficacy of Aripiprazole with that of placebo as measured by other subscales of the ABC (Social Withdrawal, Stereotypy, Hyperactivity, and Inappropriate Speech)
- To compare the Response Rate of Aripiprazole with placebo (response defined as  $\geq 25\%$  reduction from baseline in the ABC Irritability Subscale score and a CGI-I score of 1 [much improved] or 2 [very much improved])
- To compare the effect of Aripiprazole with placebo on reduction in compulsive behavior as measured by the Children's Yale-Brown Obsessive Compulsive Scale<sup>7</sup> (CY-BOCS Compulsion Scale only)

#### 3.1.2.1 Study Design

This was a double-blind, randomized, placebo-controlled, parallel-group, multicenter 8-week study designed to assess the efficacy, safety, and tolerability of Aripiprazole flexibly dosed in children and adolescents with a diagnosis of autistic disorder with serious behavioral problems characterized by irritability, agitation, and self-injurious behavior. This study consisted of a screening phase of up to 42 days followed by an 8-week treatment phase.

Patients were randomized to treatment with Aripiprazole 5 mg, 10 mg, or 15 mg/day or placebo in a 1:1:1:1 ratio. Patients who completed the 8-week treatment were eligible for an open-label long term study. There were 368 patients enrolled at 33 study centers in the United States from June 15, 2006 through March 19, 2008.

#### 3.1.2.2 Efficacy Measures

The primary efficacy measure was the mean change from baseline to Week 8 in the ABC Irritability Subscale score.

The secondary efficacy outcome measures included the mean CGI-I score, response rate (defined as  $\geq 25\%$  reduction from baseline to endpoint in the ABC Irritability Subscale score AND a CGI-I score of 1 or 2 at endpoint), and mean change from baseline to Week 8 in the CY-BOCS.

#### 3.1.2.3 Statistical Analysis Plan

For continuous measurements, such as the ABC Irritability Subscale score, data were evaluated by ANCOVA with treatment, baseline body weight (2 categories:  $\geq 40$  kg and  $< 40$  kg), study center as main effects and baseline value as a covariate for the LOCF data set. Only those

patients with both a baseline score and at least one post-baseline score will be included in the model. The models for OC data sets and subgroup analyses do not include study center.

Categorical measures such as response will be analyzed with the Cochran-Mantel Haenszel (CMH) procedure. The analyses of the LOCF data set controlled for study center and analyses of the OC data sets did not control for study center.

Except for the primary endpoint analysis, all other analyses were performed at the 5% significance level. For the primary efficacy analysis, and in order to protect the experiment-wise alpha level at 0.05 when comparing the three Aripiprazole doses versus placebo, the statistical testing will be carried out using the following sequential procedure. First the two higher Aripiprazole doses (10 mg, 15 mg) will be compared to placebo using the Hochberg procedure. Superiority to placebo will be claimed if both pairwise comparisons are significant at the 0.05 level, or one of the two is significant at the 0.025 level. Then, if both higher doses are declared statistically significant, the lower Aripiprazole dose (5 mg) will be compared to placebo and will be considered superior to placebo if the pairwise comparison is significant at the 0.05 level.

### 3.1.2.4 Patient Disposition, Demographic and Baseline Characteristics

A total of 368 subjects were enrolled into the study. Of these, 218 subjects were randomized to receive treatment. The disposition of these 218 patients is listed in Table 12.

**Table 12 Disposition of Patients**

	Treatment			
	Aripiprazole			Placebo (N=52)
	5 mg (N=53)	10 mg (N=59)	15 mg (N=54)	
Completed study	44 (83.0%)	49 (83.1%)	47 (87.0)	36 (70.6)
Terminated due to:				
Adverse event	5 (9.4%)	8 (13.6%)	4 (7.4%)	4 (7.7%)
Lost to follow up	1 (1.9%)	0	1 (1.9%)	3 (5.8%)
Lack of efficacy	0	0	0	3 (5.8%)
Subject withdrew consent	2 (3.8%)	1 (1.7%)	0	2 (3.8%)
Other	1 (1.9%)	1 (1.7%)	2 (3.9%)	2 (3.8%)

[Source: Sponsor's Table 5.1 of CSR]

Demographic characteristics for the Randomized Sample are presented by randomized group in Table 13. The mean age of the randomized patients was 9.7 years (range 6 - 17 years). Patients were predominantly male (89.4%) and white (71.1%).

**Table 13 Demographic Characteristics**

	Category	Statistic	Treatment				Total N=218
			Placebo	Aripiprazole 5 mg	Aripiprazole 10 mg	Aripiprazole 15 mg	
<b>Age (years)</b>		Mean (sd)	10.2 (3.08)	9.0 (2.83)	10.0 (3.17)	9.5 (3.11)	9.7 (3.1)
		Median	9.0	8.0	10.0	8.0	9.0
		Min - Max	6-16	6-17	6-17	6-17	6-17
<b>Gender</b>	Male	n (%)	48 (92.3)	47 (88.7)	50 (84.7)	50 (92.6)	195 (89.4)
	Female	n (%)	4 (7.7)	6 (11.3)	9 (15.3)	4 (7.4)	23 (10.6)
<b>Race</b>	White	n (%)	35 (67.3)	37 (69.8)	41 (69.5)	42 (77.8)	155 (71.1)
	Black	n (%)	13 (25.0)	13 (24.5)	15 (25.4)	9 (16.7)	50 (22.9)
	Asian	n (%)	3 (5.8)	1 (1.9)	2 (3.4)	0	6 (2.8)
	Other	n (%)	0	0	0	1 (1.9)	7 (3.2)

[Source: Sponsor's Table 5.3.1 of CSR]

### 3.1.2.5 Sponsor's Efficacy Results for Primary Endpoint

The primary endpoint was the mean change from baseline to Week 8 LOCF in the ABC Irritability Subscale score. According to the statistical analysis plan, the superiorities to placebo of all three Aripiprazole doses were established with statistically significant differences in the adjusted mean change from baseline to Week 8 in ABC Irritability Subscale score, see Table 14.

**Table 14 Mean Change from Baseline in ABC Irritability Score to Week 8 (LOCF)**

Statistics	Placebo	Arip 5mg	Arip 10mg	Arip 15mg
N	49	52	59	53
Mean Baseline (SD)	27.8 (6.5)	28.7 (7.5)	28.2 (7.4)	28.8 (6.5)
Mean change from Baseline (SD)	-7.9 (8.8)	-12.6 (10.1)	-12.9 (9.6)	-14.5 (10.9)
Treatment Differences with Placebo and 95% CI	--	-4.05 (-7.7, -0.35)	-4.82 (-8.4, -1.29)	-5.98 (-9.64, -2.32)
p-values*	--	0.0319	0.0078	0.0015

[Source: Reviewer's results]

\*p-values are nominal p-values

### 3.1.2.6 Sponsor's Other Efficacy Results

The primary analysis model was repeated using the per-protocol population. The results are summarized in Table 15. This ANCOVA model did not include study center as one of the factor. Using the Hochberg method, both Aripiprazole 15 mg and 10 mg were statistically superior to placebo. However, the lower dose (5 mg) failed to achieve the statistical significance difference from placebo.

**Table 15 Change from baseline to Week 8 in ABC Score in the OC sample**

Statistics	Placebo	Arip 5mg	Arip 10mg	Arip 15mg
N at week 8	38	44	49	45
Mean change from Baseline (SE)	-9.2 (1.5)	-12.4 (1.4)	-13.8 (1.3)	-14.4 (1.4)
Treatment Differences with Placebo and 95% CI	--	-3.2 (-7.2, 0.9)	-4.5 (-8.4, -0.6)	-5.1 (-9.2, -1.1)
p-values	--	0.124	0.022	0.013

[Source: Reviewer's results]

All the secondary analysis results can not be used to assess the statistical significances of their corresponding secondary endpoints. There is no pre-specified multiplicity adjustment to control the study-wise type I error. This reviewer verified Sponsor's results for the CGI-Improvement score, response rate, and mean change in CY-BOCS as shown in Table 16. All three Aripiprazole doses outperformed placebo numerically in all three endpoints.

**Table 16 Means and SEs for the secondary endpoints at Week 8 (LOCF)**

Statistics	Placebo	Arip 5mg	Arip 10mg	Arip 15mg
<b>CGI-I Score</b>	3.3 (.18)	2.6 (.17)	2.5 (.16)	2.5 (.17)
<b>Response Rate (N)</b>	49	52	59	53
Number of Responders	17	29	29	28
Proportions	34.7%	55.8%	49.2%	52.8%
<b>CY-BOCS Score</b>	-1.8 (.6)	-2.8 (.6)	-2.3 (.5)	-3.4 (.5)

[Source: Reviewer's results]

### 3.1.2.7 Reviewer's Results and Comments

Study CN138179 was designed to compare the efficacy of 3 fixed doses of Aripiprazole (5, 10 and 15 mg/day) with placebo in treating irritability in children and adolescents (ages 6-17 years) with a diagnosis of autistic disorder, as assessed by the mean change from baseline to endpoint (week 8) on the ABC Irritability Subscale. This reviewer confirms the findings based on the primary efficacy variable as presented in Table 6. Based on 213 evaluable subjects in the Efficacy Sample who were treated for up to 8 weeks, the mean change from baseline to Week 8 on the primary endpoint was statistically significantly greater for patients on all 3 doses of Aripiprazole versus placebo (5 mg:  $p < 0.05$ , 10 mg:  $p < 0.01$ , 15 mg:  $p < 0.001$ ).

This reviewer performed an analysis on the treatment effect over time based on an MMRM analysis. The treatment effects appeared to be consistent with the primary efficacy results, see Table 17.

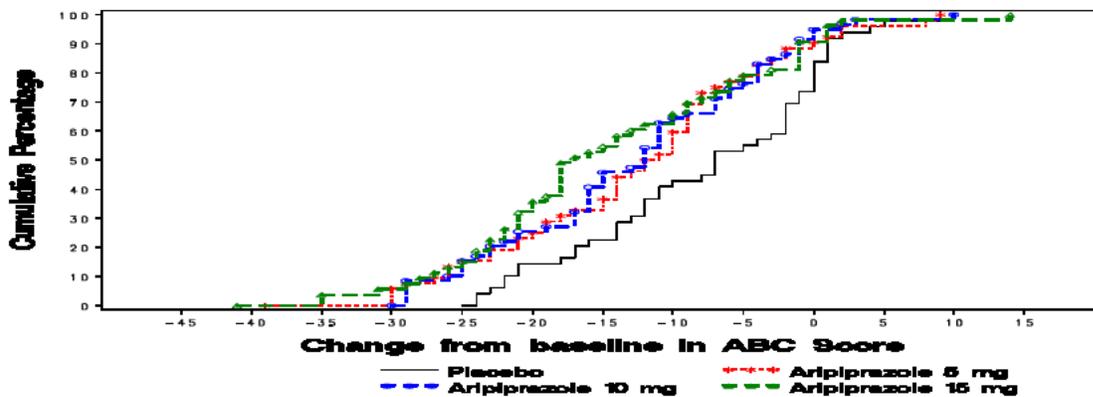
**Table 17 Change from Baseline in ABC score (MMRM) over Weeks in the ITT sample**

Visit	Aripiprazole vs Placebo					
	5 mg		10 mg		15 mg	
	Diff	p-value*	Diff	p-value*	Diff	p-value*
Week 1	-2.65	0.1764	-2.68	0.1566	-5.62	0.0041
Week 2	-6.08	0.0049	-6.34	0.0025	-5.72	0.0075
Week 3	-5.25	0.0153	-6.51	0.002	-5.08	0.075
Week 4	-4.36	0.496	-5.39	0.0124	-6.84	0.002
Week 5	-5.98	0.008	-5.15	0.0181	-6.57	0.0032
Week 6	-4.51	0.059	-6.69	0.0041	-8.58	0.0003
Week 8	-4.24	0.06	-5.17	0.0185	-7.19	0.0015

[Source: Reviewer’s results] \*p-values are not adjusted for multiplicity

Figure 3 displays the cumulative probability of these ABC Irritability Subscale score changes from baseline at Week 8 which were plotted across the range of observed values. The vertical axis indicates the proportion of patients whose score changes from baseline were less than or equal to a given number of score change (horizontal axis). For example, 50% of patients in the Aripiprazole 5, 10 and 15 mg groups had reduced the scores by up to approximately 12, 13, and 17, respectively. And 50% of patients in the Placebo group had reduced the score only by up to approximately 7. The plots suggested a separation between all three Aripiprazole doses and placebo. The cumulative distribution functions of all three Aripiprazole doses are entirely above of the distribution function of placebo, which is also consistent with the findings in Table 117. The raw means of each treatment group were generated from the LOCF data set, and were used to construct the curves in the Figure 3.

**Figure 3 Cumulative Distribution Function of the Primary Endpoint by Treatment**

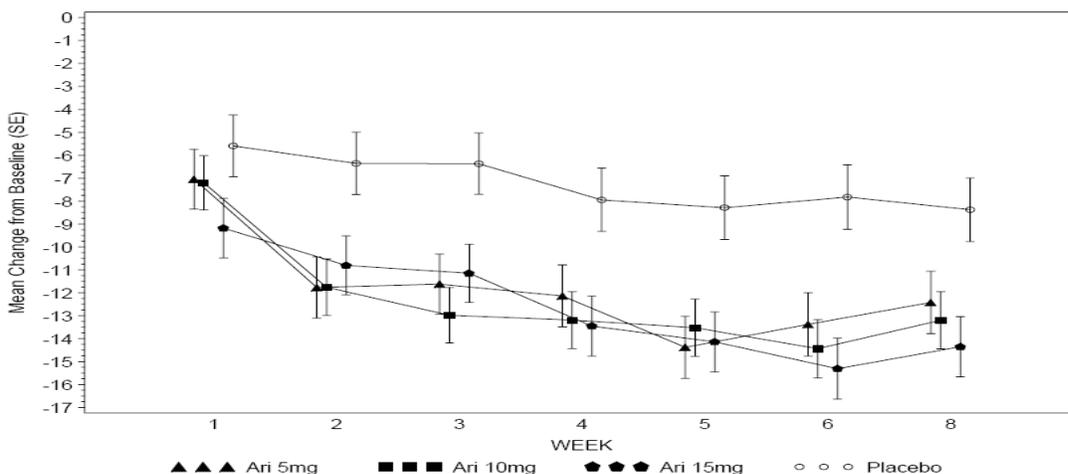


[Source: Reviewer’s Results]

The adjusted mean change from baseline is also presented in Figure 4. Model based treatment differences versus placebo in the ABC Irritability Subscale score are presented in Figure 5. Both figures corroborated the findings in Table 14. The observed changes from baseline in primary scores on all three Aripiprazole doses were consistently lower than the scores on placebo throughout the entire course of the trial. However, there were never any significant separations among the three doses.

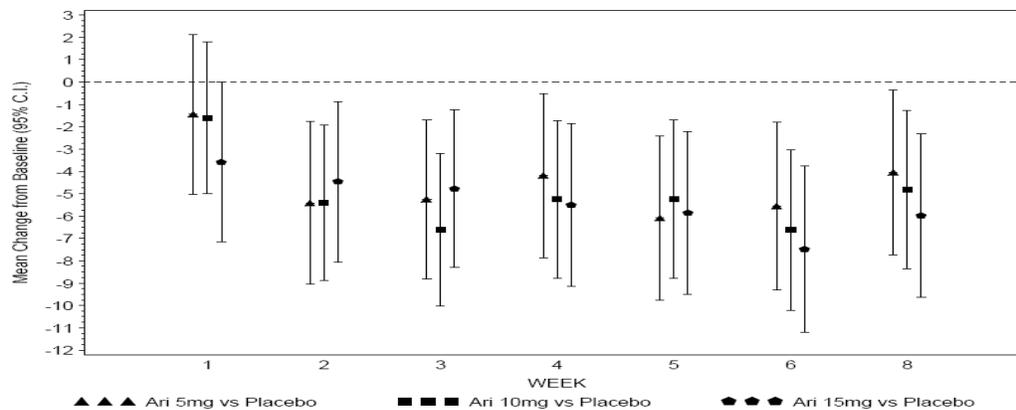
In summary, at 5-, 10-, and 15-mg/day doses, this study demonstrated the efficacy of Aripiprazole over placebo on the change from baseline to Week 8 in the ABC Irritability Subscale score.

**Figure 4 Adjusted Mean Change from Baseline in ABC Irritability Score, LOCF**



[Source: Sponsor’s Figure 7.2A]

**Figure 5 Treatment Differences in ABC Irritability Subscale Score, LOCF**



[Source: Sponsor’s Figure 7.2B]

The pairwise comparisons among the three Aripiprazole doses were drawn to explore whether the higher doses added additional benefit to the lower doses. Based on the results in Table 18, we noticed that each subsequent higher dose does add some benefit to the preceding lower doses. However, the standard error of each pairwise comparison is larger than the mean differences. Therefore, based on the results of Figure 4, Figure 5 and Table 18, the Aripiprazole 15 mg/day

group showed a numerically greatest benefit over the two lower doses; however, the difference did not appear to be statistically meaningful.

**Table 18 Pairwise Differences among the Aripiprazole Doses on Change from Baseline Scores to Week 8 (Based on Primary Statistical Model)**

Treatments	Mean Differences	Standard Error
5 mg vs. 10 mg	-0.77	1.77
5 mg vs. 15 mg	-1.93	1.82
10 mg vs. 15 mg	-1.16	1.76

[Reviewer's results]

### 3.2 Evaluation of Safety

Please refer to the clinical review for extensive safety evaluation and report. The following sections explore the effects of Aripiprazole on body weight and body mass. To explore the effects Aripiprazole on body weight, the sponsor carried out two exploratory analyses. The first analysis was on the change from baseline in body weight (in kg). The second analysis was on the change from baseline in BMI (in kg/m<sup>2</sup>). The results are summarized in Table 19 and Table 20 for both studies. Sponsor used ANCOVA model, controlling for treatment, study center, and baseline value, to obtain the treatment differences and corresponding p-values. It appears that Aripiprazole group had a significant increase in the adjustment mean change from baseline to Week 8 in patient body weight in both study. Note that the p-values are not adjusted for multiplicity. However, the differences in BMI are not as compelling as in body weight.

**Table 19 Adjusted Mean Change from Baseline in Weight and BMI, OC and LOCF, for Study CN138178**

Variable	Visit	Placebo	Aripiprazole	Treatment Difference (p-value)
		Mean (SE)	Mean (SE)	
Weight	Baseline	39.4 (2.88)	43.2 (3.01)	
	Change from baseline			
	Week 8	0.5 (0.38)	1.9 (0.35)	1.4 (0.009)
	Week 8 LOCF	0.8 (0.29)	2.0 (0.30)	1.2 (0.004)
BMI	Baseline	19.7(1.05)	20.9 (1.01)	
	Change from Baseline			
	Week 8	0.1 (0.21)	0.7 (0.19)	0.6 (0.034)
	Week 8 LOCF	0.3 (0.19)	0.7 (0.18)	0.4 (0.073)

[Source: Sponsor's table 8.10.1A and 8.10.1D, confirmed by reviewer]

In the Summary of Clinical Safety, the sponsor pooled the two study, and reconfirmed the significant differences in adjusted mean change from baseline to endpoint (LOCF) in body weight between the pooled Aripiprazole group and the pooled placebo group (1.6 kg vs. 0.4 kg, respectively). Furthermore, sponsor also concluded that the adjusted mean change from baseline

to endpoint (LOCF) in body weight Z-score was higher in the Aripiprazole group compared with the placebo group. A Z-score for body weight were derived through the algorithm provided by the CDC, which is the number of standard deviations that one is from their gender/age standardized mean.

**Table 20 Adjusted Mean Change from Baseline in Weight and BMI, OC and LOCF, for Study CN138179**

Variable	Visit	Placebo	Aripiprazole		
			5 mg	10 mg	15 mg
		Mean (SE)	Mean (SE)	Mean (SE)	Mean (SE)
Weight	Baseline	46.3 (3.21)	39.0 (3.11)	45.2 (2.90)	42.3 (3.03)
	Change from Baseline				
	Week 8	0.4 (0.37)	1.5 (0.34)	1.4 (0.33)	1.6 (0.34)
	Week 8 LOCF	0.3 (0.32)	1.3 (0.31)	1.3 (0.29)	1.5 (0.30)
	Treatment difference with placebo (p-value)				
	Week 8		1.0 (0.044)	1.0 (0.046)	1.1 (0.023)
	Week 8 LOCF		1.0 (0.024)	0.9 (0.027)	1.2 (0.007)
BMI	Baseline	21.0 (1.09)	20.2 (1.04)	21.1 (.095)	20.8 (1.03)
	Change from Baseline				
	Week 8	0.2 (0.18)	0.5 (0.17)	0.5 (0.16)	0.7 (0.17)
	Week 8 LOCF	0.2 (0.19)	0.6 (0.18)	0.6 (0.16)	0.8 (0.18)
	Treatment difference with placebo (p-value)				
	Week 8		0.3 (0.233)	0.3 (0.171)	0.5 (0.041)
	Week 8 LOCF		0.4 (0.134)	0.3 (0.189)	0.6 (0.019)

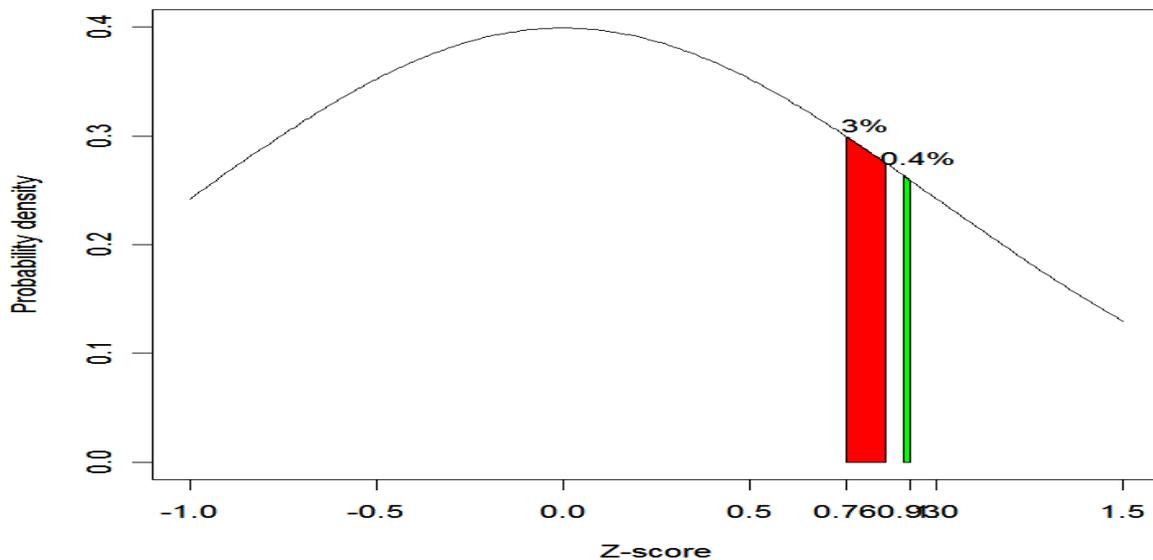
[Source: Sponsor's table 8.10.1A and 8.10.1D, confirmed by reviewer]

The agency's medical reviewer is interested in further exploring the adverse event of weight gain associated with aripiprazole treatment in pediatric autistic population and identifying potential risk factors in the pooled database. This reviewer conducted the following exploratory subgroup analyses on the mean change from baseline to the endpoint visit in body weight Z-score between the treatment groups by stratifying 1) the baseline body weight Z-score, 2) Age, and 3) Sex. The results are summarized in Table 21 and Table 22.

Overall, Aripiprazole patients and placebo patients had average baseline weight Z-score of 0.762 and 0.928 respectively, which correspond to the 77.7<sup>th</sup> and the 82.3<sup>th</sup> percentiles of their respective populations. This suggests that patients in these two studies had a heavier than normal average baseline weight. In addition, placebo patients were heavier at baseline than Aripiprazole patients. Whether the difference in baseline weight Z-score is of clinical relevancy is deferred to

the clinical review team. Aripiprazole patients increased their body weight Z-score by 0.105 standard deviations, which corresponds to an increase of the population body weight from the 77.7<sup>th</sup> percentile to the 80.7<sup>th</sup> percentile. However, the placebo group, on the other hand, reduced by 0.015 standard deviations in Z-score, which corresponds to a decrease of the population body weight from the 82.3<sup>th</sup> percentile to the 81.9<sup>th</sup> percentile. Therefore, a placebo patient on average shifted downward by 0.4%, but an Aripiprazole patient on average shifted upward by 3%, see Figure 6. The difference appears statistically significant with a nominal p-value of 0.0001. However, whether the difference is of clinical relevancy is deferred to the clinical review team.

**Figure 6** Standard Normal Distribution Density Curve



Based on the results in Table 21 and Table 22, Aripiprazole appears to have weight gain effect on the heavier and younger subjects. It is also noted that younger patients had a larger mean baseline weight Z-score compared with the other age group (0.835 versus 0.74, corresponding to the 79.8<sup>th</sup> and 77<sup>th</sup> percentiles in weight population). Upon further exploratory analysis, the pooled data seems to suggest that baseline weight Z-score and age group more or less contributed to the treatment differences in change from baseline at the endpoint visit in body weight Z-score. It is, however, uncertain whether the impact is clinical relevant.

**Table 21 Subgroup by Baseline Body Weight Z-score**

Body Weight Z-score Percentile	Variable	Endpoint	Body Weight Z-score				Treatment Comparison (a)			
			Placebo		Aripiprazole		Diff	95% CI	P-value	
			N	Mean	N	Mean				
Overall	Baseline		98	0.928	209	0.762	-0.17	-0.47, 0.14	0.29	
	Change from Baseline to Endpoint	OC	71	-0.027	176	0.116	0.143	0.07, 0.22	0.0001	
		LOCF	98	-0.015	209	0.105	0.119	0.06, 0.145	0.0001	
< 25%	Change from Baseline to Endpoint	OC	3	0.11	26	0.048	-0.10	-0.63, 0.42	0.693	
		LOCF	5	0.0235	31	0.0244	-0.03	-0.40, 0.34	0.872	
25-50%		OC	13	-0.079	20	0.178	0.29	0.07, 0.52	0.0129	
		LOCF	19	-0.025	29	0.150	0.22	0.04, 0.41	0.0192	
50-75%		OC	11	0.018	37	0.157	0.17	-0.09, 0.44	0.196	
		LOCF	18	0.035	47	0.144	0.12	-0.07, 0.31	0.214	
75-100%		OC	43	-0.03	85	0.11	0.16	0.09, 0.236	<0.0001	
		LOCF	55	-0.03	94	0.102	0.15	0.08, 0.219	<0.0001	
< 40%		Change from Baseline to Endpoint	OC	9	-0.048	37	0.097	0.187	-0.13, 0.51	0.242
			LOCF	15	-0.005	46	0.082	0.144	-0.09, 0.378	0.225
40-60%	OC		9	-0.04	25	0.17	0.196	-0.045, 0.44	0.107	
	LOCF		13	-0.013	35	0.144	0.155	-0.03, 0.34	0.0967	
60-90%	OC		24	-0.022	50	0.145	0.22	0.062, 0.384	0.007	
	LOCF		32	-0.028	58	0.133	0.12	0.068, 0.335	0.0035	
90-100%	OC		28	-0.023	56	0.088	0.12	0.048, 0.184	0.0011	
	LOCF		37	-0.01	62	0.078	0.09	0.026, 0.155	0.0065	
< 50%	Change from Baseline to Endpoint		OC	16	-0.04	46	0.104	0.20	-0.016, 0.42	0.0695
			LOCF	24	-0.015	60	0.085	0.16	-0.01, 0.32	0.068
≥50%		OC	54	-0.023	122	0.125	0.16	0.08, 0.245	0.0002	
		LOCF	73	-0.016	141	0.116	0.14	0.07, 0.24	0.0001	

[Source: Reviewer's Results] \*p-values are not adjusted for multiplicity

(a) ANOCVA model, with treatment as a main effect, protocol as a stratification effect and Baseline weight Z-score as covariate. 95% confidence intervals for the differences and the p-values for pairwise comparisons are based on ANCOVA model.

**Table 22 Subgroup by Age and Sex**

Age Subgroup	Variable	Population	Body Weight Z-score				Treatment Comparison		
			Placebo		Aripiprazole		Diff	95% CI	P-value
			N	Mean	N	Mean			
6-12		OC	56	-0.015	140	0.155	0.188	0.098, 0.278	<0.0001
		LOCF	77	0.005	165	0.140	0.154	0.076, 0.232	<0.0001
13-17	Change	OC	15	-0.069	36	-0.036	0.041	-0.11, 0.192	0.5855
		LOCF	21	-0.087	44	-0.027	0.068	-0.05, 0.188	0.2626
Sex Subgroup	Variable	Population	Body Weight Z-score				Treatment Comparison		
			Placebo		Aripiprazole		Diff	95% CI	P-value
			N	Mean	N	Mean			
Male		OC	63	-0.023	156	0.117	0.159	0.073, 0.246	0.0004
		LOCF	88	-0.013	185	0.106	0.140	0.068, 0.213	0.0002
Female	Change	OC	8	-0.059	20	0.113	0.205	0.013 0.398	0.038
		LOCF	10	-0.030	24	0.093	0.145	-0.035, 0.325	0.1101

[Source: Reviewer’s Analysis]

## 4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

### 4.1 Gender, Age and Race group

#### 4.1.1 STUDY CN138178

##### 4.1.1.1 Gender

There are 87.8% of all patients were males. Aripiprazole appeared to improve the ABC subscale for both males and females. There are no noticeable differences between two genders.

**Table 23 Subgroup Analysis for ABC Subscale Score by Gender**

Subgroup	Aripiprazole	Placebo
<b>Male</b>		
No. Subjects	41	43
Mean (SD)	-11.6 (11.1)	-4.6 (8.1)
<b>Female</b>		
No. Subjects	5	6
Mean (SD)	-15.0 (4.4)	-6.2 (15.7)

[Source: reviewer's result]

##### 4.1.1.2 Age

Age at entry was dichotomized to  $\leq 12$  versus  $> 12$  years old. Aripiprazole appeared to improve the ABC subscale for both age groups. It also appeared to be more efficacious for the subjects under the age of 12 years. However, it should be noted that this age group accounted for more than 85% of the subjects. The results are summarized in Table 24.

**Table 24 Subgroup Analysis for ABC Subscale Score by Age**

Subgroup	Aripiprazole	Placebo
<b>Age group (6-12)</b>		
No. Subjects	36	44
Mean (SD)	-12.6 (11.0)	-4.4 (9.1)
<b>Age group (13-17)</b>		
No. Subjects	10	5
Mean (SD)	-9.6 (8.9)	-7.8 (10.0)

[Source: Reviewer's result]

##### 4.1.1.3 Race

Due to possible small sample sizes for certain ethnic groups, race was categorized into White, Black, and Other. Aripiprazole appeared to show numerical improvement in the primary endpoint in all three race groups, see Table 25. However, it should be noted that very few patients were in the Black and Other categories.

**Table 25 Subgroup Analysis for ABC Subscale Score by Race**

Subgroup	Aripiprazole	Placebo
<b>Race = White</b>		
No. Subjects	32	39
Mean (SD)	-12.3 (10.4)	-5.1 (9.2)
<b>Race = Black</b>		
No. Subjects	11	7
Mean (SD)	-11.4 (11.8)	-1.7 (7.4)
<b>Race = Other</b>		
No. Subjects	3	3
Mean (SD)	-10.7 (11.6)	-7.7 (13.9)

[Source: Reviewer's results]

**4.1.2 STUDY CN138179****4.1.2.1 Gender**

Table 26 shows the reviewer's subgroup analysis results on ABC subscale scores for gender. The number of patients by gender group is very comparable and the mean change from baseline stratified by gender appeared consistent with the primary result. All three Aripiprazole doses had numerical favorable results than placebo group in both gender, except the 15 mg/day female group. It could be explained by the very low enrollment in female subjects.

**Table 26 Subgroup Analysis for ABC Subscale Score by Gender**

Subgroup	Arip 5 mg	Arip 10 mg	Arip 15 mg	Placebo
<b>Male</b>				
No. Subjects	46	50	49	45
Mean (SD)	-12.7 (10.7)	-12.9 (9.6)	-15.0 (11.1)	-7.8 (9.0)
<b>Female</b>				
No. Subjects	6	9	4	4
Mean (SD)	-12.3 (3.7)	-12.8(9.8)	-8.5 (7.9)	-8.8 (7.7)

[Source: Reviewer's results]

**4.1.2.2 Age**

Table 27 shows the reviewer's subgroup analysis results on ABC subscale scores for Age group. Age at entry was dichotomized to  $\leq 12$  versus  $> 12$  years old. The number of patients by age group is very comparable and the mean change from baseline stratified by age appeared consistent with the primary result. All three Aripiprazole doses had numerical favorable results than placebo group in both age groups.

**Table 27 Subgroup Analysis for ABC Subscale Score by Age**

Subgroup	Aripiprazole 5 mg	Aripiprazole 10 mg	Aripiprazole 15 mg	Placebo
<b>Age group (6-12)</b>				
No. Subjects	43	45	42	33
Mean (SD)	-11.5 (10.2)	-11.8 (9.6)	-13.6 (10.4)	-7.5 (8.9)
<b>Age group (13-17)</b>				
No. Subjects	9	14	11	16
Mean (SD)	-18.1 (8.0)	-16.5 (8.6)	-18.0 (12.8)	-8.5 (8.8)

[Source: Reviewer's results]

**4.1.2.3 Race**

Table 28 shows the reviewer's subgroup analysis results on ABC subscale scores for Race group. Due to possible small sample sizes for certain ethnic groups, race was categorized into White, Black, and Other. The number of patients by race group is very comparable and the mean change from baseline stratified by race appeared consistent with the primary result. All three Aripiprazole doses had numerical favorable results than placebo group in White and Black patients. Aripiprazole 10 mg had poor performance in the Other group, it could be due to the lack of enrollment in this race group.

**Table 28 Subgroup Analysis for ABC Subscale Score by Race**

Subgroup	Aripiprazole 5 mg	Aripiprazole 10 mg	Aripiprazole 15 mg	Placebo
<b>Race = White</b>				
No. Subjects	36	41	41	33
Mean (SD)	-12.4 (11.3)	-13.5 (9.62)	-14.2 (11.2)	-7.4 (8.7)
<b>Race = Black</b>				
No. Subjects	13	15	9	12
Mean (SD)	-12.5 (7.0)	-13.3 (9.5)	-15.9 (11.7)	-8.2 (9.1)
<b>Race = Other</b>				
No. Subjects	3	3	3	4
Mean (SD)	-16.3 (7.8)	-2.7 (4.2)	-15.0 (6.2)	-10.5 (10.5)

[Source: Reviewer's result]

**4.2 Other Subgroup Populations**

The entire patient population was enrolled within United States, so the comparison between U.S. and Non-U.S. sites can not be analyzed. Furthermore, no other subgroups were analyzed.

## **5 SUMMARY AND CONCLUSIONS**

### **5.1 Statistical Issues and Collective Evidence**

Both studies were positive on the primary endpoints. In study CN138178, the efficacy of Aripiprazole flexibly doses (2 to 15 mg/day) versus placebo in the adjusted mean change from baseline on the ABC Irritability Subscale at the endpoint visit (Week 8 LOCF) was demonstrated. In addition, Aripiprazole flexible dose also demonstrated statistically significant improvement compared with placebo on the key secondary efficacy endpoint, the clinician rated CGI-I score at the endpoint visit (Week 8 LOCF). In study CN138179, the efficacy of Aripiprazole at 5-, 10-, and 15-mg/day doses versus placebo in the adjusted mean change from baseline on the ABC Irritability Subscale at the endpoint visit (Week 8 LOCF) was demonstrated with three statistically significant p-values.

### **5.2 Conclusions and Recommendations**

The sponsor's Aripiprazole autistic disorder program consisted of 2 placebo-controlled studies of identical design except that fixed dosing was used for one (CN138179) and flexible dosing for the other (CN138178).

In the flexible-dose study (CN138178), Aripiprazole demonstrated statistically significant efficacy relative to placebo in treating irritability in children and adolescents (ages 6-17 years) with a diagnosis of autistic disorder, as assessed by the mean change from baseline on the ABC Irritability Subscale at Week 8. Aripiprazole also produced statistically significant improvements over placebo on the key secondary efficacy measure, the CGI-I score, at Week 8.

The fixed-dose study CN138179 evaluated target Aripiprazole doses of 5, 10 and 15 mg/day. All 3 dose groups demonstrated significantly greater efficacy than placebo in treating irritability in children and adolescents (ages 6-17 years) with a diagnosis of autistic disorder, as measured by the mean change from baseline to Week 8 on the ABC Irritability Subscale.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21436	SUPPL-27	OTSUKA PHARMACEUTICA L CO LTD	ABILIFY (ARIPRAZOLE) 10/15/20/30MG

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/s/

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STEVE G BAI  
10/08/2009

PEILING YANG  
10/08/2009

KOOROS MAHJOOB  
10/08/2009

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 21-436/S027**

**OTHER REVIEW(S)**

**M E M O R A N D U M**

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

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**CLINICAL INSPECTION SUMMARY**

**DATE:** September 3, 2009

**TO:** Kofi Ansah, Regulatory Project Manager  
Jin Zhang, M.D., Medical Officer  
Division of Psychiatry Products, HFD-130

**THROUGH:** Tejashri Purohit-Sheth, MD, FAAAI  
Branch Chief  
Good Clinical Practice Branch II  
Division of Scientific Investigations

**FROM:** Anthony Orenca, MD, FACP  
Medical Officer  
Good Clinical Practice Branch II  
Division of Scientific Investigations

**SUBJECT:** Evaluation of Clinical Inspections

**NDA:** 21-436/SE1-27

**APPLICANT:** BMS

**DRUG:** Abilify (aripiprazole) tablets (NME:No)

**THERAPEUTIC CLASSIFICATION:** Standard Review

**INDICATION:** Treatment of irritability associated with autistic disorder in patients aged 6-17 years.

**CONSULTATION REQUEST DATE:** March 4, 2009; March 18, 2009 (DFS-signed)

**DIVISION ACTION GOAL DATE:** August 21, 2009

**PDUFA DATE:** November 21, 2009

## I. BACKGROUND:

Aripiprazole (Abilify) is an atypical antipsychotic, approved drug as oral formulations for several psychiatric indications, including (1) treatment of schizophrenia in adults and adolescents aged 13 – 17 years, (2) treatment of manic or mixed episodes associated with Bipolar I Disorder as monotherapy or adjunctive to lithium or valproate in adults and pediatric patients aged 10-17 years, (3) adjunctive treatment of Major Depressive Disorder in adults. BMS submitted an efficacy supplement SE1-27 to support their new indication for the treatment of irritability associated with autism disorder targeting the pediatric population, aged 6-17 years.

The sites selected for inspection were: Dr. Melmed (Phoenix, AZ); Dr. Attala (Smyrna, GA); Dr. Hardan (Stanford, CA); and Dr. Rugino (Toms River, NJ). In the consult as outlined by the Medical Officers and review team, and discussions with DPP, there were potential issues about patient recruitment and the potential impact on efficacy results, and adherence to the inclusion and exclusion criteria for autism. In addition to the reasons for selected sites above, the higher enrolling clinical sites in Georgia (Site 16) and California (Site 17) were specifically identified by the review team due to the potential of these sites to drive primary efficacy results. Two protocols were audited: CN13179 for the Arizona, Georgia, and California sites, and CN138178 for the New Jersey clinical study site.

## II. RESULTS (by protocol/site):

Name of CI and site #, if known	City, State	Protocol	Insp. Date	EIR Received Date	Final Classification
Ashraf Attala, M.D., Site 016	Smyrna, GA	CN138-179	July 14, 2009	Pending	Pending Preliminary classification NAI
Antonio Hardan, M.D. Site 017	Stanford, CA	CN-138-179	Pending	Pending	Pending Preliminary classification NAI
Raun Melmed, M.D. Site 004	Phoenix, AZ	CN138-179	May 12 – 26, 2009	June 16, 2009	NAI
Thomas A. Rugino, M.D. Site 022	Toms River, NJ	CN138-178	April 22 – May 5, 2009	June 8, 2009	VAI

### Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.

VAI-Response Requested = Deviation(s) form regulations. See specific comments below for data acceptability

OAI = Significant deviations for regulations. Data unreliable.

Preliminary: The EIR has not been received and findings are based on preliminary communication with the field.

## **A. PROTOCOL #CN138179**

### **1. Raun Melmed, M.D./Site #4**

Southwest Autism Research and Resource Center  
300 North 18th Street  
Phoenix, AZ 85006

#### **a. What was inspected?**

The inspection was conducted in accordance with Compliance Program 7348.811, from May 12 to 26, 2009. A total of 21 subjects who consented were screened with five subjects designated as screen failures. There were 16 study subjects who were randomized; 13 patients took the study drug; 10 patients subsequently completed the study and five subjects were listed as lost to follow-up. The inspection evaluated the following documents: source records of the study subjects, case report forms, study drug accountability logs, study monitoring visits and correspondence. Source documents were verified for consistency with data listings.

#### **b. Limitations of inspection**

None.

#### **c. General observations/commentary**

The inspection process reviewed the inclusion and exclusion criteria, Informed Consent Forms, and drug accountability records. All subjects at Dr. Melmed's site were verified to have been enrolled as per study protocol, as to whether patients had CGI-S score of 4 or greater, an ABC Irritability Subscale score of 18 or greater at Visit 1 or Visit 1a (screening) and baseline visit (randomization), and a documented mental age of 18 months or greater.

No Form FDA 483 was issued. There were instances of minor record keeping errors with drug accountability records. For example, the identity of the study staff receiving returned drug or empty container was not always appropriately documented on the source record; there were minor issues with documentation of drug reconciliation (although there is no concern that subjects received appropriate randomized therapy); and inadequate documentation that parents were reminded to bring back drug "containers" during their next visit.

Another issue that was identified dealt with the inability of the site to consistently obtain orthostatic blood pressures. The protocol required a blood pressure and pulse measurement lying for five minutes and again after standing for two minutes. It was not possible to obtain these for all subjects with autism owing to their behavior and irritability features. The principal investigator (PI) discussed this issue with the sponsor multiple times at monthly meetings, and noted similar concerns by other participating P.I.'s; however, the sponsor maintained the requirements for obtaining vital signs for autistic study subjects.

**d. Data acceptability/reliability for consideration in the NDA review decision.**

Although minor issues were noted, it is unlikely that these would impact data integrity. The data in support of clinical efficacy and safety at this clinical site appears acceptable.

**2. Antonio Hardan, M.D./Site 17**

Child and Adolescent Psychiatry Clinic  
Stanford University School of Medicine  
401 Quarry Road  
Stanford, CA 94305

**a. What was inspected?**

The inspection was conducted in accordance with Compliance Program 7348.811, with a preliminary report issued by the field District Office in San Francisco, California on September 3, 2009, for inspection that was conducted the week of August 31, 2009. A total of 21 subjects who consented were screened, 16 subjects were enrolled and randomized and 13 subjects completed the study. There were 5 screen failures and 3 randomized subjects had early terminations.

Source documents were verified for consistency with data listings.

**b. Limitations of inspection**

None.

**c. General observations/commentary: Preliminary findings** (for inspected records)

No FDA-483 was issued and no significant record irregularities were documented.

**d. Data acceptability/reliability for consideration in the NDA review decision:**

Based on preliminary communication with the field investigator, the data appear reliable.

*Note: Observations noted above are based on preliminary communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.*

**3. Ashraf Attala, M.D./Site #16**

Institute for Behavioral Medicine  
4015 South Cobb Drive SE Suite 120  
Symrna, GA 33080

**a. What was inspected?**

The inspection was conducted in accordance with Compliance Program 7348.811, with a preliminary report issued by the field District Office in Atlanta on July 14, 2009. A total of 45 subjects who consented were screened; 26 subjects were enrolled; 23 subjects

completed the study. All 45 study participant records were checked for informed consent. For the 26 subjects enrolled and randomized in the study, records were reviewed for even-numbered study subjects and spot-checked for odd-numbered study subjects.

The inspection evaluated the following documents: source records of the study subjects, case report forms, study drug accountability logs, study monitoring visits and correspondence. Source documents were verified for consistency with data listings.

**b. Limitations of inspection**

None.

**c. General observations/commentary: Preliminary findings** (FDA Form 483 was not issued):

- Protocol deviations, similar to the other Clinical Investigators in CN138179, involved lack of cooperation of study participants in blood pressure and other vital sign readings.
- No deaths or hospitalizations and no evidence of under-reporting adverse events.
- Consistency in the primary efficacy endpoint data in the case report form and NDA submission materials provided to the field investigators.

**d. Data acceptability/reliability for consideration in the NDA review decision:**

Based on preliminary communication with the field investigator, the data appear reliable.

*Note: Observations noted above are based on preliminary communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.*

**B. PROTOCOL #CN13878**

**1. Thomas Rugino, M.D./Site #4**

Children's Specialized Hospital  
94 Stevens Road  
Toms River, NJ 08755

**a. What was inspected?**

The inspection was conducted in accordance with Compliance Program 7348.811, from April 22 to May 5, 2009. A total of 17 subjects were screened and 11 subjects were randomized. The inspection evaluated the following documents: source records of the study subjects, case report forms, study drug accountability logs, study monitoring visits and correspondence. Source documents were verified for consistency with data listings.

**b. Limitations of inspection**

None.

**c. General observations/commentary**

At the end of the inspection, a Form FDA-483 was issued. The issues noted are summarized below:

- Not following the investigational plan. Specifically, Subjects #78031, #78035, #78063 and #78064 did not have clonidine discontinued, and Subject #78035 did not have risperidone discontinued per study protocol.
- Consent form deficiencies. Specifically, parent of Subject #78113 did not sign version 091007 of the consent form until September 26, 2007. Study medication and related procedures were conducted on September 20, 2007.
- Inaccurate or inadequate case histories. Five (5) of 11 subjects had discrepancies between source documents, or between source documents and case report forms (CRFs). Specifically, for Subjects #78050, #78056, #78063, #78109 and #78113, respectively. These deficiencies were conveyed to the Clinical Investigator in a Voluntary Action Indicated (VAI) letter, and are considered unlikely to impact data integrity.

**d. Data acceptability/reliability for consideration in the NDA review decision.**

Upon review of the Establishment Inspection Report, Form FDA 483, and as specified in the Note to the Review Division in the letter issued to Dr. Rugino dated May 14, 2009, inadequate inaccuracies in study subjects' records and study protocol violations observed during the field inspection are unlikely to affect data integrity. DSI defers to DPP for further evaluation of the overall clinical impact in lack of discontinuation of "prohibited medications at least four days before screening," per study protocol, in the conduct of this clinical trial for the subjects referenced above.

**III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS**

Four clinical investigator sites have been inspected in support of this application. Results, to include preliminary results, received from the four sites (Dr. Melmen, Dr. Rugino, Dr. Hardan and Dr. Attala) documented adherence to Good Clinical Practices regulations governing the conduct of clinical investigations. No significant discrepancies were noted with the data listings provided in the NDA and source documents at the clinical sites. The data generated by these three sites appear reliable in support of the application.

**Note: Observations noted above for Dr. Hardan and Dr. Attala are based on preliminary communications with the field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the EIR.**

*{See appended electronic signature page}*

Anthony Orenca, M.D.  
Medical Officer  
Good Clinical Practice Branch II  
Division of Scientific Investigations

CONCURRENCE:

*{See appended electronic signature page}*

Tejashri Purohit-Sheth, M.D.  
Branch Chief  
Good Clinical Practice Branch II  
Division of Scientific Investigations

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

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ANTHONY J ORENCIA  
09/04/2009

TEJASHRI S PUROHIT-SHETH  
09/04/2009

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**NDA 21-436/S027**

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

## EXCLUSIVITY SUMMARY

NDA # 021436

SUPPL # 027

HFD # 130

Trade Name ABILIFY

Generic Name Aripiprazole

Applicant Name Otsuka Pharmaceutical Company Ltd.

Approval Date, If Known 11/19/2009

### **PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?**

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

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES  NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

SE1

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

YES  NO

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

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

d) Did the applicant request exclusivity?

YES  NO

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

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

YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

NO

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

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

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES  NO

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

NDA#	21436	ABILIFY oral tablets
NDA#	21866	ABILIFY intramuscular injection
NDA#	21713	ABILIFY oral solution
	21729	ABILIFY oral disintegrating tablets

2. Combination product.

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

YES  NO

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

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)  
IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a)

is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES  NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

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

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

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

YES  NO

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

YES  NO

If yes, explain:

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

YES  NO

If yes, explain:

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

The efficacy of aripiprazole in improving symptoms of irritability in children and adolescents with autistic disorder was demonstrated by positive results obtained from two 8-week, randomized, multicenter, double-blind, placebo-controlled studies (CN138178 and CN138179).

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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

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

Investigation #1 YES  NO

Investigation #2 YES  NO

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

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

Investigation #1 YES  NO



identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1  
!  
!  
YES  ! NO   
Explain: ! Explain:

Investigation #2  
!  
!  
YES  ! NO   
Explain: ! Explain:

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

YES  NO

If yes, explain:

=====

Name of person completing form: Kofi Ansah, Pharm.D.  
Title: Senior Regulatory Project Manager  
Date: 11/13/09

Name of Office/Division Director signing form: Thomas Laughren, M.D.  
Title: Director, Division of Psychiatry Product

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-21436	SUPPL-27	OTSUKA PHARMACEUTICA L CO LTD	ABILIFY (ARIPRAZOLE) 10/15/20/30MG

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

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/s/

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KOFI B ANSAH

11/19/2009

This summary review was done with and cleared through Paul.

THOMAS P LAUGHREN

11/19/2009

**NDA NO. 21-436**

**ABILIFY® (ARIPIPRAZOLE BMS-337039/OPC-14597)**

Treatment of Irritability Associated with Autistic Disorder in Pediatric Patients

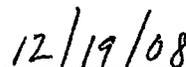
Aged 6-17 years

**CERTIFICATION: DEBARRED PERSONS**

As required by Section 306(k)(1) of the Federal Food, Drug and Cosmetics Act, Bristol-Myers Squibb Company certifies that it has not used and will not use in any capacity the services of any person listed as debarred under Section 306 (a) or (b) of the Federal Food, Drug and Cosmetics Act in connection with this Application.



\_\_\_\_\_  
Marianne Frost  
Associate Director, Global Regulatory Sciences  
Bristol-Myers Squibb Company  
5 Research Parkway  
Wallingford, CT 06492  
203-677-6143



\_\_\_\_\_  
Certification Date

## ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 021436 BLA #	NDA Supplement # 027 BLA STN #	If NDA, Efficacy Supplement Type: SE-1
Proprietary Name: ABILIFY Established/Proper Name: Aripiprazole Dosage Form: 2mg, 5mg, 10mg, 15mg, 20mg, & 30mg		Applicant: Otsuka Pharmaceutical Company Ltd. Agent for Applicant (if applicable): Otsuka Pharmaceutical Development & Commercialization, Inc.
RPM: Kofi Ansah, Pharm.D.		Division: Division of Psychiatry Products
<p><b>NDA:</b> NDA Application Type: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>		<p><b>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</b> Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p><b>Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.</b></p> <p><input type="checkbox"/> No changes      <input type="checkbox"/> Updated Date of check:</p> <p><b>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</b></p> <p><b>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</b></p>
❖ User Fee Goal Date Action Goal Date (if different)		11/21/09
❖ Actions		
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions ( <i>specify type and date for each action taken</i> )		<input checked="" type="checkbox"/> None
❖ Promotional Materials ( <i>accelerated approvals only</i> ) Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a> ). If not submitted, explain _____		<input type="checkbox"/> Received

<sup>1</sup> The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application Characteristics <sup>2</sup>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority          Chemical classification (new NDAs only):</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch  <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch  <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDAs: Subpart H <span style="margin-left: 200px;">BLAs: Subpart E</span>  <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <span style="margin-left: 100px;"><input type="checkbox"/> Accelerated approval (21 CFR 601.41)</span>  <input type="checkbox"/> Restricted distribution (21 CFR 314.520) <span style="margin-left: 100px;"><input type="checkbox"/> Restricted distribution (21 CFR 601.42)</span>          Subpart I <span style="margin-left: 200px;">Subpart H</span>  <input type="checkbox"/> Approval based on animal studies <span style="margin-left: 100px;"><input type="checkbox"/> Approval based on animal studies</span></p> <p><input type="checkbox"/> Submitted in response to a PMR  <input type="checkbox"/> Submitted in response to a PMC</p> <p>Comments: _____</p>	
❖ Date reviewed by PeRC ( <i>required for approvals only</i> ) If PeRC review not necessary, explain: _____	10/14/2009
❖ BLAs only: <i>RMS-BLA Product Information Sheet for TBP</i> has been completed and forwarded to OBPS/DRM ( <i>approvals only</i> )	<input type="checkbox"/> Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 ( <i>approvals only</i> )	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications ( <i>approvals only</i> )	
• Office of Executive Programs (OEP) liaison has been notified of action	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Press Office notified of action (by OEP)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Indicate what types (if any) of information dissemination are anticipated	<input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

<sup>2</sup> All questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> <li>NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date exclusivity expires:
<ul style="list-style-type: none"> <li>NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #      and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> <li>Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> <li>Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.</li> </ul>	21 CFR 314.50(i)(1)(i)(A) <input checked="" type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</li> </ul>	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For <b>each paragraph IV</b> certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i></li> </ul>	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes       No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes       No

If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "**No**," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes       No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes       No

If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "**No**," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
<b>CONTENTS OF ACTION PACKAGE</b>	
❖ Copy of this Action Package Checklist <sup>3</sup>	Yes
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
<b>Action Letters</b>	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Action(s) and date(s) AP Letter/Labeling
<b>Labeling</b>	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)</li> </ul>	
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	
<ul style="list-style-type: none"> <li>• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable</li> </ul>	
❖ Medication Guide/Patient Package Insert/Instructions for Use ( <i>write submission/communication date at upper right of first page of each piece</i> )	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	

<sup>3</sup> Fill in blanks with dates of reviews, letters, etc.  
Version: 8/26/09

<ul style="list-style-type: none"> <li>Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)</li> </ul>	
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	
<ul style="list-style-type: none"> <li>Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable</li> </ul>	
❖ Labels ( <b>full color</b> carton and immediate-container labels) ( <i>write submission/communication date on upper right of first page of each submission</i> )	
<ul style="list-style-type: none"> <li>Most-recent division proposal for (only if generated after latest applicant submission)</li> </ul>	
<ul style="list-style-type: none"> <li>Most recent applicant-proposed labeling</li> </ul>	
❖ Proprietary Name <ul style="list-style-type: none"> <li>Review(s) (<i>indicate date(s)</i>)</li> <li>Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> </ul>	
❖ Labeling reviews ( <i>indicate dates of reviews and meetings</i> )	<input type="checkbox"/> RPM <input type="checkbox"/> DMEDP <input type="checkbox"/> DRISK <input type="checkbox"/> DDMAC <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
<b>Administrative / Regulatory Documents</b>	
❖ Administrative Reviews (e.g., RPM Filing Review <sup>4</sup> /Memo of Filing Meeting) ( <i>indicate date of each review</i> )	03/25/2009
❖ NDAs only: Exclusivity Summary ( <i>signed by Division Director</i> )	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	
<ul style="list-style-type: none"> <li>Applicant in on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>This application is on the AIP <ul style="list-style-type: none"> <li>If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
❖ Pediatric Page ( <i>approvals only, must be reviewed by PERC before finalized</i> )	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent ( <i>include certification</i> )	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications ( <i>letters (except previous action letters), emails, faxes, telecons</i> )	
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
<ul style="list-style-type: none"> <li>PeRC (<i>indicate date of mtg; approvals only</i>)</li> </ul>	<input type="checkbox"/> Not applicable 10/14/2009
<ul style="list-style-type: none"> <li>Pre-Approval Safety Conference (<i>indicate date of mtg; approvals only</i>)</li> </ul>	<input type="checkbox"/> Not applicable
<ul style="list-style-type: none"> <li>Regulatory Briefing (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> No mtg
<ul style="list-style-type: none"> <li>Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> <li>EOP2 meeting (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> No mtg 12/7/2004

<sup>4</sup> Filing reviews for scientific disciplines should be filed behind the respective discipline tab.  
Version: 8/26/09

<ul style="list-style-type: none"> <li>Other (e.g., EOP2a, CMC pilot programs)</li> </ul>	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> <li>Date(s) of Meeting(s)</li> <li>48-hour alert or minutes, if available (<i>do not include transcript</i>)</li> </ul>	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input type="checkbox"/> None
<b>Clinical Information<sup>5</sup></b>	
❖ Clinical Reviews	
<ul style="list-style-type: none"> <li>Clinical Team Leader Review(s) (<i>indicate date for each review</i>)</li> <li>Clinical review(s) (<i>indicate date for each review</i>)</li> <li>Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)</li> </ul>	10/30/2009 <input type="checkbox"/> None
❖ Safety update review(s) ( <i>indicate location/date if incorporated into another review</i> )	
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	
❖ Clinical reviews from other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> Not needed
❖ Risk Management <ul style="list-style-type: none"> <li>REMS Document and Supporting Statement (<i>indicate date(s) of submission(s)</i>)</li> <li>REMS Memo (<i>indicate date</i>)</li> <li>Review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> </ul>	<input checked="" type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) ( <i>include copies of DSI letters to investigators</i> )	<input type="checkbox"/> None requested 09/04/2009
<b>Clinical Microbiology</b> <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
Statistical Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 10/08/2009
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None

<sup>5</sup> Filing reviews should be filed with the discipline reviews.  
Version: 8/26/09

Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ DSI Clinical Pharmacology Inspection Review Summary <i>(include copies of DSI letters)</i>	<input checked="" type="checkbox"/> None
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Supervisory Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary <i>(include copies of DSI letters)</i>	<input checked="" type="checkbox"/> None requested
<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
• Product quality review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 09/23/2009
• ONDQA Biopharmaceutics review <i>(indicate date for each review)</i>	
• BLAs only: Facility information review(s) <i>(indicate dates)</i>	<input type="checkbox"/> None
❖ Microbiology Reviews	
• NDAs: Microbiology reviews (sterility & pyrogenicity) <i>(indicate date of each review)</i>	<input type="checkbox"/> Not needed
• BLAs: Sterility assurance, product quality microbiology <i>(indicate date of each review)</i>	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	09/23/2009
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
• NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
• BLAs: ○ TBP-EER	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation

○ Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) ( <i>date completed must be within 60 days prior to AP</i> )	Date completed: <input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold
❖ NDAs: Methods Validation	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input checked="" type="checkbox"/> Not needed

## Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

-----  
NDA-21436

-----  
SUPPL-27

-----  
OTSUKA  
PHARMACEUTICA  
L CO LTD

-----  
ABILIFY (ARIPRAZOLE)  
10/15/20/30MG

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

KOFI B ANSAH  
11/19/2009

**From:** [Ansah, Kofi](#)  
**To:** ["Frost, Marianne";](#)  
**cc:** [Goldberger, David; Behling, Susan;](#)  
**Subject:** RE: NDA 21-436/S-027 - Abilify/Autism - BMS/Otsuka Labeling Edits 11-18-09  
**Date:** Thursday, November 19, 2009 12:52:40 PM

---

Dear Marianne,

We acknowledge your response -- thank you. We are in agreement on the labeling changes for NDA 021436/S-027 - ABILIFY.

Regards,  
Kofi.

---

**From:** Frost, Marianne [mailto:marianne.frost@bms.com]  
**Sent:** Thursday, November 19, 2009 8:44 AM  
**To:** Ansah, Kofi  
**Cc:** Goldberger, David; Behling, Susan  
**Subject:** RE: NDA 21-436/S-027 - Abilify/Autism - BMS/Otsuka Labeling Edits 11-18-09

Dear Kofi,  
Thank you for the information. We are in agreement.  
Best regards,  
Marianne

---

**From:** Ansah, Kofi [mailto:Kofi.Ansah@fda.hhs.gov]  
**Sent:** Thursday, November 19, 2009 8:31 AM  
**To:** Frost, Marianne  
**Cc:** Goldberger, David; Behling, Susan  
**Subject:** RE: NDA 21-436/S-027 - Abilify/Autism - BMS/Otsuka Labeling Edits 11-18-09

Dear Marianne,

This modification is acceptable. Both Highlights and 1.3 will read:

"..... was established in two 6-week trials in adults with MDD who had an inadequate response to antidepressant therapy during the current episode."

So, I think we now have an agreement. Please confirm that we are in agreement, ASAP.

Thanks,  
Kofi.

---

**From:** Frost, Marianne [mailto:marianne.frost@bms.com]  
**Sent:** Wednesday, November 18, 2009 6:34 PM  
**To:** Ansah, Kofi  
**Cc:** Goldberger, David; Behling, Susan  
**Subject:** RE: NDA 21-436/S-027 - Abilify/Autism - BMS/Otsuka Labeling Edits 11-18-09

Dear Kofi,

We are in agreement with the changes except for the MDD Indication:

(b) (4)

Abilify is indicated for use as an adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD). Efficacy was established in two 6-week trials in adults with MDD who had an inadequate response to antidepressant therapy during the current episode.

If this proposal is not acceptable, we should plan to meet at 9 Am tomorrow. Please let me know as soon as possible.

Best regards,  
Marianne

---

**From:** Ansah, Kofi [mailto:Kofi.Ansah@fda.hhs.gov]  
**Sent:** Wednesday, November 18, 2009 4:38 PM  
**To:** Frost, Marianne

**Cc:** Goldberger, David; Behling, Susan

**Subject:** RE: NDA 21-436/S-027 - Abilify/Autism - BMS/Otsuka Labeling Edits 11-18-09

Dear Marianne,

Please find attached our revisions to your proposed labeling following receipt and review of your Autism-Resp2-aripi-pro (2).doc [and the markup.doc] you submitted this afternoon. We have used track changes with bracketed comments to explain our changes. The changes are all in highlights, Indication and Use, and Dosage and Administration. Please review and let us know if we have an agreement by the end of today.

Thanks,  
Kofi.

---

*Kofi Boadu Ansah, R.Ph., Pharm.D.*

CDR, US Public Health Service

Regulatory Project Manager, Division of Psychiatry Products

FDA/Center for Drug Evaluation and Research, Office of Drug Evaluation-I

10903 New Hampshire Avenue, White Oak Bldg 22, Room 4109

Silver Spring, MD 20993 - 0002

Phone: (301) 796-4158

Fax: (301) 796-9838

Email: [Kofi.Ansah@fda.hhs.gov](mailto:Kofi.Ansah@fda.hhs.gov)

*Commissioned Corps of the United States Public Health Service- "Protecting, promoting, and advancing the health and safety of the Nation"*

---

**From:** Frost, Marianne [mailto:marianne.frost@bms.com]

**Sent:** Wednesday, November 18, 2009 12:55 PM

**To:** Ansah, Kofi

**Cc:** Goldberger, David; Behling, Susan

**Subject:** NDA 21-436/S-027 - Abilify/Autism - BMS/Otsuka Labeling Edits 11-18-09

Dear Kofi,

As discussed during our teleconference yesterday, please find attached our revisions to the FDA labeling provided on 11-4-09. Please note that we removed caps throughout the label for major depressive disorder, bipolar I disorder, schizophrenia, bipolar mania and autistic disorder but this is not shown in track changes.

This e-mail will be followed up with a formal submission to NDA 21-436 via e-gateway by tomorrow.

Best regards,  
Marianne



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This message (including any attachments) may contain confidential, proprietary, privileged and/or private information. The information is intended to be for the use of the individual or entity designated above. If you are not the intended recipient of this message, please notify the sender immediately, and delete the message and any attachments. Any disclosure, reproduction, distribution or other use of this message or any attachments by an individual or entity other than the intended recipient is prohibited.

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This message (including any attachments) may contain confidential, proprietary, privileged and/or private information. The information is intended to be for the use of the individual or entity designated above. If you are not the intended recipient of this message, please notify the sender immediately, and delete the message and any attachments. Any disclosure, reproduction, distribution or other use of this message or any attachments by an individual or entity other than the intended recipient is prohibited.

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Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

-----  
NDA-21436

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SUPPL-27

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OTSUKA  
PHARMACEUTICA  
L CO LTD

-----  
ABILIFY (ARIPRAZOLE)  
10/15/20/30MG

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

KOFI B ANSAH  
11/19/2009

**From:** [Ansah, Kofi](#)  
**To:** ["Frost, Marianne";](#)  
**cc:** [George.hemsworth@otsuka.com](mailto:George.hemsworth@otsuka.com);  
**Subject:** NDA 21-436/ S-027 - ABILIFY -- REQUEST FOR STATISTICAL INFORMATION [10-22-09]  
**Date:** Thursday, October 22, 2009 10:37:54 AM

---

Dear Ms. Frost,

Regarding your supplemental NDA [NDA 21-436/ S-027] currently under review, the division is further exploring the excess weight gain associated with Aripiprazole. Please submit the dataset which produced the Table 2.1.5.7B-7 and Appendix 2.1.5.7B-9. The dataset should include study number, patient id, baseline weight and z-score, <=3 month change from baseline body weight and z-score, 3-6 month change from baseline body weight and z-score, 6-9 month change from baseline body weight and z-score, and >9 month change from baseline body weight and z-score. Please include the baseline results into the Table 2.1.5.7B-7 and Appendix 2.1.5.7B-9.

Please provide this information as soon as possible (preferably by 11:00 am E.S.T on 10/26/09.

Thanks,  
Kofi.

---

***Kofi Boadu Ansah, R.Ph., Pharm.D.***

CDR, US Public Health Service

Regulatory Project Manager, Division of Psychiatry Products

FDA/Center for Drug Evaluation and Research, Office of Drug Evaluation-I  
10903 New Hampshire Avenue, White Oak Bldg 22, Room 4109

Silver Spring, MD 20993 - 0002

Phone: (301) 796-4158

**Email: [Kofi.Ansah@fda.hhs.gov](mailto:Kofi.Ansah@fda.hhs.gov)**

Application  
Type/Number

Submission  
Type/Number

Submitter Name

Product Name

-----  
NDA-21436

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SUPPL-27

-----  
OTSUKA  
PHARMACEUTICA  
L CO LTD

-----  
ABILIFY (ARIPRAZOLE)  
10/15/20/30MG

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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KOFI B ANSAH  
10/24/2009

**From:** [Ansah, Kofi](#)  
**To:** ["Frost, Marianne";](#)  
**cc:** ["Mallikaarjun, Kusuma";](#)  
**Subject:** NDA 21-436 (S-027)/  
OTSUKA/ ABILIFY (ARIPIPRAZOLE)/ AUTISM -- INFORMATION REQUEST  
**Date:** Monday, August 31, 2009 12:25:07 PM

---

Dear Ms. Frost,

Regarding your sNDA [NDA 21-436/ S-027] currently under review, we are interested in further exploring adverse event of weight gain associated with aripiprazole treatment in pediatric autistic population and identifying potential risk factors. We request that you provide the following information:

1. Please provide an electronic data set for the flexible dose (CN138178) and fixed dose (CN138179) studies. The derived data set should include one row for each patient's id, the study number, age, gender, treatment dose/group, baseline height, baseline weight and z-score, Week 8 weight and z-score for both observed (missing if dropped out) and imputed cases (LOCF), baseline BMI and z-score. In addition, please also provide raw data which contains patient's id, the study number and all available Visits' weights and z-scores.
2. We note that you have provided tables (Appendix 2.1.5.7A) summarizing body weight z-scores and BMI z-scores. Please provide the reference (algorithm, formula, etc.) you used to derive the z-scores, and the SAS program along with the data sets that produced the results in these tables. If this information has been included in your NDA submission, please provide the detailed location.

Please provide the requested information within 2 weeks [i.e. by COB on September 14, 2009].

Thanks,  
Kofi.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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KOFI B ANSAH  
08/31/2009

**From:** [Ansah, Kofi](#)  
**To:** ["Frost, Marianne";](#)  
**Subject:** RE: NDA 21-436 (SE1-027)/ ABILIFY (ARIPIPRAZOLE)/ AUTISM -- INFO REQUEST [STUDY SITES]  
**Date:** Friday, March 27, 2009 2:15:40 PM

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Hi Marianne,

Thank you for your quick response. Yes, this information would help DPP and DSI move forward with the inspection assignments for the ORA field investigator for this supplement.

Thanks,  
Kofi.

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**From:** Frost, Marianne [mailto:[marianne.frost@bms.com](mailto:marianne.frost@bms.com)]  
**Sent:** Thursday, March 26, 2009 1:32 PM  
**To:** Ansah, Kofi  
**Cc:** Mallikaarjun, Kusuma; Behling, Susan  
**Subject:** RE: NDA 21-436 (SE1-027)/ ABILIFY (ARIPIPRAZOLE)/ AUTISM -- INFO REQUEST [STUDY SITES]

Kofi,  
Please find the information requested below. Can you confirm if this information is needed for the DSI audits?

Best regards,  
Marianne

**Raun Melmed, M.D.**

Southwest Autism Research and Resource Center  
300 North 18th Street  
Phoenix, AZ 85006  
Phone: 602-340-8717  
Fax: 602-340-8720  
Other: [raun.melmed@melmedcenter.com](mailto:raun.melmed@melmedcenter.com)

Study Coordinator: [REDACTED] (b) (4)

Phone: [REDACTED] (b) (4)

Fax: 602-340-8720

e-mail: (b) (4)@autismcenter.org

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**Ashraf Attalla, M.D**

Institute for Behavioral Medicine  
4015 South Cobb Drive SE  
Suite 120  
Smyrna, GA 30080  
Phone: 770-319-8013  
Fax: 770-319-8021  
e-mail: [md@ashrafattalla.com](mailto:md@ashrafattalla.com)

*Study Coordinator:* (b) (4)

Phone: 770-319-8013

Fax: 770-319-8021

e-mail: (b) (4)[ashrafattalla.com](mailto:ashrafattalla.com)

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**Antonio Hardan, M.D.**

Stanford University School of Medicine  
Child & Adolescent Psychiatry Clinic  
401 Quarry Road  
Stanford, CA 94305  
Phone: 650-724-8919  
Fax: 650-723-8552  
e-mail: [hardanay@stanford.edu](mailto:hardanay@stanford.edu)

*Study Coordinator:* (b) (4)

Phone: (b) (4)

Fax: 650-723-8552

e-mail (b) (4)[@stanford.edu](mailto:@stanford.edu)

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**Thomas A. Rugino, MD**

Children's Specialized Hospital

94 Stevens Road

Toms River, NJ 08755

Phone: 732-797-3826

Fax: 732-797-3812

e-mail: [trugino@childrens-specialized.org](mailto:trugino@childrens-specialized.org)

**Study Coordinator:** [REDACTED] (b) (4)

Phone : [REDACTED] (b) (4)

Fax: 732-797-3812

e-mail [REDACTED] (b) (4) [@childrens-specialized.org](mailto:[REDACTED]@childrens-specialized.org)

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**From:** Ansah, Kofi [mailto:Kofi.Ansah@fda.hhs.gov]

**Sent:** Thursday, March 26, 2009 10:03 AM

**To:** Frost, Marianne

**Subject:** NDA 21-436 (SE1-027)/ ABILIFY (ARIPRAZOLE)/ AUTISM -- INFO REQUEST [STUDY SITES]

Dear Marianne:

Good morning. Regarding your supplemental NDA application for aripiprazole in Autism, could you please provide or add the updated/most current contact numbers (phone and fax), if any, for the following Study Sites.

**Name of CI/Address/contact information**

Raun Melmed, M.D.

Southwest Autism Research and Resource Center

300 North 18th Street

Phoenix, AZ 85006

Phone:

Fax:

Other:

Ashraf Attalla, M.D.  
Institute for Behavioral Medicine  
4015 South Cobb Drive SE  
Suite 120  
Smyrna, GA 30080  
Phone:  
Fax:  
Other:

Antonio Hardan, M.D.  
Stanford University School of Medicine  
Child & Adolescent Psychiatry Clinic  
401 Quarry Road  
Stanford, CA 94305  
Phone:  
Fax:  
Other:

Thomas A. Rugino, MD  
Children's Specialized Hospital  
94 Stevens Road  
Toms River, NJ 08755  
Phone:  
Fax:  
Other:

Please let me know if you have any questions regarding this request and email me your response as soon as you can.

Thanks,  
Kofi.

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

-----  
Kofi B Ansah  
3/30/2009 12:54:40 PM  
CSO

**NDA REGULATORY FILING REVIEW**  
**(Including Memo of Filing Meeting)**

NDA # 22-436 Supplement # 027 Efficacy Supplement Type SE- 1

Proprietary Name: Abilify  
Established Name: Aripiprazole  
Strengths: 2mg, 5mg, 10mg, 15mg, 20mg, & 30mg

Applicant: Otsuka Pharmaceutical Company Ltd.  
Agent for Applicant (if applicable): Otsuka Pharmaceutical Development & Commercialization, Inc.

Date of Application: 01/21/09  
Date of Receipt: 01/21/09  
Date clock started after UN:  
Date of Filing Meeting: 03/2/09  
Filing Date: 03/22/09  
Action Goal Date (optional): User Fee Goal Date: 21-NOV-09

Indication(s) requested: Irritability Associated with Autistic Disorders

Type of Original NDA: (b)(1)  (b)(2)   
AND (if applicable)  
Type of Supplement: (b)(1)  (b)(2)

**NOTE:**

(1) *If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.*

Review Classification: S  P   
Resubmission after withdrawal?  Resubmission after refuse to file?   
Chemical Classification: (1,2,3 etc.)  
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES  NO

User Fee Status: Paid  Exempt (orphan, government)   
Waived (e.g., small business, public health)

**NOTE:** *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES  NO

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES  NO
- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES  NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES  NO   
If yes, explain:
- If yes, has OC/DMPQ been notified of the submission? YES  NO
- Does the submission contain an accurate comprehensive index? YES  NO   
If no, explain:
- Was form 356h included with an authorized signature? YES  NO   
**If foreign applicant, both the applicant and the U.S. agent must sign.**
- Submission complete as required under 21 CFR 314.50? YES  NO   
If no, explain:
- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES
2. This application is an eNDA or combined paper + eNDA YES   
This application is: All electronic  Combined paper + eNDA   
This application is in: NDA format  CTD format   
Combined NDA and CTD formats

- Does the eNDA, follow the guidance?  
(<http://www.fda.gov/cder/guidance/2353fnl.pdf>) YES  NO

**If an eNDA, all forms and certifications must be in paper and require a signature.**

If combined paper + eNDA, which parts of the application were submitted in electronic format?

Additional comments:

3. This application is an eCTD NDA. YES   
**If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.**

Additional comments:

• Patent information submitted on form FDA 3542a? YES  NO

• Exclusivity requested? YES, 3 Years NO

*NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

• Correctly worded Debarment Certification included with authorized signature? YES  NO   
**If foreign applicant, both the applicant and the U.S. Agent must sign the certification.**

*NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . ."*

• Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES  NO

• If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES  NO

• Is this submission a partial or complete response to a pediatric Written Request? YES  NO

If yes, contact PMHT in the OND-IO

• Financial Disclosure forms included with authorized signature? YES  NO   
**(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)**

*NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.*

• Field Copy Certification (that it is a true copy of the CMC technical section) YES  NO

• PDUFA and Action Goal dates correct in tracking system? YES  NO   
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

• Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

• List referenced IND numbers: IND 42,776; IND 67,380; IND 71,501; IND 73,863; IND 76,132

• Are the trade, established/proper, and applicant names correct in COMIS? YES  NO   
If no, have the Document Room make the corrections.

• End-of-Phase 2 Meeting(s)? Date(s) 07-DEC-2004 NO   
If yes, distribute minutes before filing meeting.

• Pre-NDA Meeting(s)? Date(s) Preliminary Comments accepted by sponsor and meeting cancelled NO   
If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) \_\_\_\_\_ NO   
If yes, distribute letter and/or relevant minutes before filing meeting.

**Project Management**

- If Rx, was electronic Content of Labeling submitted in SPL format? YES  NO   
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:  
Was the PI submitted in PLR format? YES  NO

If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES  NO
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES  NO
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?  
N/A  YES  NO
- Risk Management Plan consulted to OSE/IO? N/A  YES  NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA  YES  NO

**If Rx-to-OTC Switch or OTC application:**

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES  NO
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES  NO

**Clinical**

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES  NO

**Chemistry**

- Did applicant request categorical exclusion for environmental assessment? YES  NO   
If no, did applicant submit a complete environmental assessment? YES  NO   
If EA submitted, consulted to EA officer, OPS? YES  NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES  NO
- If a parenteral product, consulted to Microbiology Team? YES  NO

ATTACHMENT

**MEMO OF FILING MEETING**

DATE: 2 March, 2009

NDA #: 21-436/ SE1-027

DRUG NAMES: Abilify (Aripiprazole)

APPLICANT: Otsuka Pharmaceutical Company, Ltd.

BACKGROUND: This supplemental application proposes the following change(s): irritability associated with autism in pediatric patients aged 6-17 years.

ATTENDEES:

Thomas Laughren, M.D.	Director, Division of Psychiatry Products (DPP)
Mitchell Mathis, M.D.	Deputy Director, DPP
Gwen Zornberg, M.D.	Medical Team Leader, DPP
Jing Zhang, M.D.	Medical Reviewer
Barry Rosloff, Ph.D.	Pharmacology/Toxicology Supervisor
Aisar Atrakchi, Ph.D.	Pharmacology/Toxicology Team Leader
Sonia Tabacova, Ph.D.	Pharmacology/Toxicology Reviewer
Chidambaram Nallaperum, Ph.D.	Pharmaceutical Assessment Lead
Peiling Yang, Ph.D.	Team Leader, Office of Biostatistics
Yeh-Fong Chen, Ph.D.,	Statistical Reviewer
Kofi Ansah, Pharm.D.	Regulatory Project Manager

ASSIGNED REVIEWERS (including those not present at filing meeting) :

**Discipline/Organization**

**Reviewer**

Medical:

Jing Zhang, M.D.

Secondary Medical:

Statistical:

Steve Bai, Ph.D.

Pharmacology:

Sonia Tabacova, Ph.D.

Statistical Pharmacology:

Chemistry:

Chidambaram Nallaperum, Ph.D.

Environmental Assessment (if needed):

Biopharmaceutical:

Microbiology, sterility:

Microbiology, clinical (for antimicrobial products only):

DSI:

Anthony Orenca

OPS:

Regulatory Project Management:

Kofi Ansah, Pharm.D.

Other Consults:

Per reviewers, are all parts in English or English translation? YES  NO   
If no, explain:

CLINICAL FILE  REFUSE TO FILE   
 • Clinical site audit(s) needed? YES  NO   
 If no, explain:  
 • Advisory Committee Meeting needed? YES, date if known \_\_\_\_\_ NO   
 • If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A  YES  NO

CLINICAL MICROBIOLOGY N/A  FILE  REFUSE TO FILE

STATISTICS N/A  FILE  REFUSE TO FILE

BIOPHARMACEUTICS FILE  REFUSE TO FILE   
 • Biopharm. study site audits(s) needed? YES  NO

PHARMACOLOGY/TOX N/A  FILE  REFUSE TO FILE   
 • GLP audit needed? YES  NO

CHEMISTRY FILE  REFUSE TO FILE   
 • Establishment(s) ready for inspection? YES  NO   
 • Sterile product? YES  NO   
 If yes, was microbiology consulted for validation of sterilization? YES  NO

ELECTRONIC SUBMISSION:  
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:  
**(Refer to 21 CFR 314.101(d) for filing requirements.)**

- The application is unsuitable for filing. Explain why:
- The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
  - No filing issues have been identified.
  - Filing issues to be communicated by Day 74. List (optional):

**ACTION ITEMS:**

1.  Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
2.  If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
3.  If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
4.  If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
5.  Convey document filing issues/no filing issues to applicant by Day 74.

Kofi Ansah, Pharm.D.  
Regulatory Project Manager

## Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

- (1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
- (2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),
- (2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.
- (3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

- (2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or
- (3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

**Appendix B to NDA Regulatory Filing Review  
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES  NO

If “No,” skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):
3. Is this application for a drug that is an “old” antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.) YES  NO

If “Yes,” skip to question 7.

4. Is this application for a recombinant or biologically-derived product? YES  NO

If “Yes “contact your ODE’s Office of Regulatory Policy representative.

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.
- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved? YES  NO

*(Pharmaceutical equivalents* are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and (3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If “No,” to (a) skip to question 6. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES  NO

- (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES  NO

If “Yes,” (c), list the pharmaceutical equivalent(s) and proceed to question 6.

If “No,” to (c) list the pharmaceutical equivalent and contact your ODE’s Office of Regulatory Policy representative.

Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES  NO

*(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)*

*If “No,” to (a) skip to question 7. Otherwise, answer part (b and (c)).*

- (b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES  NO

- (c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES  NO

*If “Yes,” to (c), proceed to question 7.*

**NOTE:** *If there is more than one pharmaceutical alternative approved, consult your ODE’s Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.*

*If “No,” to (c), list the pharmaceutical alternative(s) and contact your ODE’s Office of Regulatory Policy representative. Proceed to question 7.*

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES  NO

*If “No,” skip to question 8. Otherwise, answer part (b).*

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, “This application provides for a new indication, otitis media” or “This application provides for a change in dosage form, from capsules to solution”).

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)).) YES  NO

10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES  NO

11. Is the application for a duplicate of a listed drug whose only difference is YES  NO

that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9).

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES  NO

13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

- Not applicable (e.g., solely based on published literature. See question # 7)
- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)  
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)  
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)  
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)  
Patent number(s):

**NOTE:** *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.*

- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).  
Patent number(s):
- Written statement from patent owner that it consents to an immediate effective date upon approval of the application.  
Patent number(s):
- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)  
Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

YES  NO

*If "Yes," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug*

*Was this listed drug product(s) referenced by the applicant? (see question # 2)*

YES  NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

N/A  YES  NO

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES  NO

If "Yes," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

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/s/

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Kofi B Ansah  
3/25/2009 11:06:23 AM  
CSO



**DEPARTMENT OF HEALTH & HUMAN SERVICES**

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

**FILING COMMUNICATION**

NDA 21-436/S-027

Otsuka Pharmaceutical Company, Ltd.  
Attention: Kusuma Mallikaarjun, Ph.D.  
Senior Director, Regulatory Affairs  
Otsuka Pharmaceutical Development and Commercialization, Inc.  
2440 Research Boulevard  
Rockville, MD 20850

Dear Dr. Mallikaarjun:

Please refer to your January 21, 2009 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Abilify (aripiprazole) tablets 2mg, 5mg, 10mg, 15mg, 20mg and 30mg.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed under section 505(b) of the Act on March 22, 2009 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, contact LCDR Kofi Ansah, Regulatory Project Manager, at (301)796-4158.

Sincerely,

*{See appended electronic signature page}*

Thomas Laughren, M.D.  
Director  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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/s/

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Thomas Laughren  
3/20/2009 10:41:54 AM

# DSI CONSULT: Request for Clinical Inspections

**Date:** March 4, 2009

**To:** Tejashri Purohit-Sheth, M.D., Branch Chief, GCP2, HFD-47  
Division of Scientific Investigations, HFD-47  
Office of Compliance/CDER

**Through:** Thomas Laughren, M.D./Director/Division of Psychiatry Products/HFD-130  
Gwen Zornberg, M.D./Medical Team Leader

**From:** Kofi Ansah, Pharm.D., Senior Regulatory Project Manager  
Division of Psychiatry Products/ HFD-130

**Subject:** **Request for Clinical Site Inspections**

## **I. General Information**

Application#: NDA 21-436 S027

Sponsor/Sponsor contact information:

Marianne Frost

Associate Director, Global Regulatory Science, BMS

Otsuka Pharmaceutical Development and Commercialization, Inc.

Telephone: (203) 677-6143

Email: Marianne.Frost@bms.com

Drug: Abilify (Aripiprazole)

NME: No

Standard or Priority: Standard

Study Population < 18 years of age: Pediatric Patients 6 – 17 years of age

Pediatric exclusivity: Yes

PDUFA: 21-Nov-2009

Action Goal Date: 21-Sep-2009

**Inspection Summary Goal Date: 21-Aug-2009**

## **II. Background Information**

This is a supplemental NDA for aripiprazole's indication in the treatment of irritability associated with autistic disorder in patients aged 6 – 17 years.

This submission includes two positive short-term clinical trials:

DSI Updated 12/2007

CN138178

A multiple center, double-blind, randomized, placebo-controlled, flexible-dosed, parallel-group, 8-week study. This study was conducted in 20 US centers from 15-Jun-2006 to 28-Apr-2008. Aripiprazole dose range in this study was 2-15 mg/d. Ninety-eight patients (6 to 17 year old) were randomized (1:1, Arip : placebo). The completion rate in total was 76.5%.

The primary endpoint: the mean change from baseline to endpoint in the Aberrant Behavior Checklist (ABC) irritability subscale score

The key secondary endpoint: the mean change in Clinical Global Impression (CGI) score

Efficacy Conclusion: Aripiprazole demonstrated statistically significant improvement compared with placebo on the primary and key secondary endpoints at week 8.

Safety Conclusion: There was no evidence of new safety concerns.

CN138179

A multiple center, double-blind, randomized, placebo-controlled, fixed-dosed, parallel-group, 8-week study. This study was conducted in 37 US centers from 15-Jun-2006 to 03-Jun-2008. Aripiprazole doses in this study were 5, 10 and 15 mg/d. Two hundred and eighteen patients (age 6 to 17) were randomized (1:1:1:1, Arip 5, 10, 15 and placebo). The completion rate in total was 81.7%.

The primary endpoint: the mean change from baseline to endpoint in ABC irritability subscale score

Efficacy Conclusion: Aripiprazole at all dose groups (5, 10 and 15 mg) demonstrated statistically significant improvement compared with placebo on the primary and key secondary endpoints at week 8.

Safety Conclusion: There was no evidence of new safety concerns.

### **III. Protocol/Site Identification**

See the Table below for Protocol Title/# for all protocols to be audited.

<b>Site # (Name,Address, Phone number, email, fax#)</b>	<b>Protocol #</b>	<b>Number of Subjects</b>	<b>Indication</b>
Attala, Ashraf, M.D., and (b) (4) Institute for Behavioral Medicine 4015 South Cobb Drive SE Suite 120 Smyrna, GA 30080  Site # 016	CN138- 179	26	Irritability Associated with Autistic Disorder
Hardan, Antonio, MD Stanford Univ. School of Medicine Child & Adolescent Psychiatry Clinic 401 Quarry Road Stanford, CA 94305  Site #017	CN138- 179	16	Irritability Associated with Autistic Disorder
Melmed, Raun, MD Southwest Autism Research and Resource Center 300 North 18 <sup>th</sup> Street Phoenix, AZ 85006  Site #004	CN138- 179	14	Irritability Associated with Autistic Disorder
Thomas A. Rugino, MD Children's Specialized Hospital 94 Stevens Road Toms River, NJ 08755  Site #22	CN138- 178	11	Irritability Associated with Autistic Disorder

Please find a copy of the clinical study report and the study protocol at EDR Location:

[\\FDSWA150\NONECTD\N21436\S\\_027\2009-01-21](\\FDSWA150\NONECTD\N21436\S_027\2009-01-21)

#### **IV. Site Selection/Rationale**

Site #016 and #017 in Study CN138179 are chosen because they are large sites (26 and 16 patients, respectively) in this study and the data from this site drive the efficacy results of the study.

**Domestic Inspections:**

Reasons for inspections (please check all that apply):

- Enrollment of large numbers of study subjects
- High treatment responders (specify):
- Significant primary efficacy results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- Other (specify):

**International Inspections:**

Reasons for inspections (please check all that apply):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other (specify)

Should you require any additional information, please contact LCDR Kofi Ansah, Pharm.D. at Ph: 301-796-4158 or Name of Jing Zhang, M.D. at Ph: 301-796-1927.

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/s/

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Thomas Laughren  
3/18/2009 02:51:32 PM



NDA 21-436/S-027

**NDA ACKNOWLEDGMENT**

Otsuka Pharmaceutical Company, Ltd.  
Attention: Kusuma Mallikaarjun, Ph.D.  
Senior Director, Regulatory Affairs  
Otsuka Pharmaceutical Development and Commercialization, Inc.  
2440 Research Boulevard  
Rockville, MD 20850

Dear Dr. Mallikaarjun:

We have received your new drug application (NDA) submitted pursuant to section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Abilify (aripiprazole) tablets 2mg, 5mg, 10mg, 15mg, 20mg and 30mg

Date of Application: January 21, 2009

Date of Receipt: January 21, 2009

Our Reference Number: NDA 21-436/S-027

This supplemental application proposes the following change(s): irritability associated with autism in pediatric patients aged 6-17 years.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on March 22, 2009 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be November 21, 2009.

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Psychiatry Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/cder/ddms/binders.htm>.

If you have any questions please call me at (301) 796-4158.

Sincerely,

*{See appended electronic signature page}*

LCDR Kofi Ansah, Pharm.D.  
Senior Regulatory Project Manager  
Division of Psychiatry Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

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Kofi B Ansah  
3/18/2009 02:50:47 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>		
TO (Division/Office): <b>HFD- 710/Stat</b> Attention: Peiling Yang		FROM: HFD-130/ Division of Psychiatry Products		
DATE 2/13/09	IND NO. 71,501 (Autism) 42,776 (Schizo)	NDA NO. 21-436 (SE5-027)	TYPE OF DOCUMENT NDA Efficacy Supplement	DATE OF DOCUMENT 1/21/09
NAME OF DRUG Aripiprazole (OCP-14597, BMS-337039, Abilify) Tablets		PRIORITY CONSIDERATION Standard 10 Months	CLASSIFICATION OF DRUG Autism	DESIRED COMPLETION DATE <b>Filing Meeting: 3/2/09</b> <b>PDUFA: 11/21/09</b>
NAME OF FIRM: OTSUKA Pharmaceuticals Co., Inc.				
<b>REASON FOR REQUEST</b>				
<b>I. GENERAL</b>				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input checked="" type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):				
<b>II. BIOMETRICS</b>				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): New NDA Efficacy Supplement		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
<b>III. BIOPHARMACEUTICS</b>				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
<b>IV. DRUG EXPERIENCE</b>				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
<b>V. SCIENTIFIC INVESTIGATIONS</b>				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: This is a new NDA Efficacy Supplement for the use of Aripiprazole in Autism. You reviewed the related IND (71501) as part of a Pre-sNDA meeting request/ package [later cancelled by the sponsor]. The Filing Meeting is on 3/2/09 at 3:00pm. The medical reviewer is Jing Zhang, M.D. and the TL is Gwen Zornberg, M.D. Please let me know if you have any questions to send to the sponsor. Thanks, Kofi. The network location is : <a href="\\FDSWA150\NONECTD\N21436\S 027\2009-01-21">\\FDSWA150\NONECTD\N21436\S 027\2009-01-21</a>				
SIGNATURE OF REQUESTER Kofi Ansah, Pharm.D. Senior Regulatory Project Manager 301-796-4158 Kofi.ansah@fda.hhs.gov		METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input checked="" type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

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Kofi B Ansah

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