Exhibit 1

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF MARYLAND

Otsuka Pharmaceutical Co., Ltd., et al.,	*	
Plaintiff,	*	
v.	*	
Sylvia Mathews Burwell, et al.	*	CIVIL ACTION NO.
Defendants.	*	

* * * * * * * *

DECLARATION OF ROBERT D. MCQUADE, Ph.D.

Robert D. McQuade, Ph.D. states as follows under penalty of perjury:

1. I am over 18 years of age and am competent to testify to the matters herein. This declaration is based on my personal knowledge and is submitted in support of plaintiffs' motion for summary judgment.

2. My current position at Otsuka America Pharmaceutical, Inc. ("OAPI") is Executive Vice President and Chief Strategic Officer. In this role, I am responsible for direct management of the U.S. Medical Affairs organization and for the broad development of strategy for Otsuka's U.S. pharmaceutical business, including both commercial and development strategies. I have been with Otsuka for about 10.5 years. I have knowledge about the corporate operations of Otsuka Pharmaceutical Co., Ltd. ("OPC"), Otsuka Pharmaceutical Development & Commercialization, Inc. ("OPDC"), and OAPI.

3. I have a Ph.D. in Biochemistry from the University of North Carolina (1986). I have over 30 years of experience in the pharmaceutical industry; my previous employers were Schering-Plough Corp. and Bristol-Myers Squibb Co.

Otsuka's Brand Drug Abilify

4. OPC owns the New Drug Applications for aripiprazole – N021436 (tablets), N021729 (orally disintegrating tablets), N021713 (oral solution), N021866 (injection; intramuscular) – which Otsuka markets under the brand name Abilify®. OPC manufactures Abilify tablets. OPC is headquartered in Tokyo, Japan and, through its sales of Abilify, conducts substantial business in the District of Maryland and the United States.

5. OPDC conducts research for OPC on Abilify and has been designated to be the company's agent in negotiations with FDA. OPDC is the entity that received the "corrected" approval letter from FDA on February 24, 2015. *See* Ex. A.

6. OAPI distributes and markets Abilify.

7. FDA first approved Abilify on November 15, 2002, then for schizophrenia. FDA has since approved Abilify for schizophrenia in adolescents, acute treatment of manic and mixed episodes associated with Bipolar I Disorder in both adult and pediatric patients, irritability associated with autistic disorder in pediatric patients, and as an add-on treatment for depression in adults.

8. Otsuka extends rebates to government programs (Medicaid, Tricare, Medicare Part D, and Veterans Affairs programs) to lower the cost of Abilify.

9. Abilify is covered by patent and regulatory protection in the United States, some of which expire on April 20, 2015.

Otsuka's sNDA

10. In 2005, Dr. Floyd R. Sallee, M.D., Ph.D., requested from FDA orphan drug designation for aripiprazole "for the treatment of Tourette Syndrome in children and adolescents." That application sought orphan drug designation based on an estimate that the target population of U.S. school age children with Tourette's Disorder was 120,000. Ex. B.

11. In 2006, FDA granted orphan drug designation for the use of aripiprazole for the treatment of Tourette's Disorder. Otsuka subsequently acquired that designation. Among other things, this designation means that Otsuka is entitled to a seven-year period of market exclusivity, running from the date of FDA's approval of an orphan drug indication. During that seven-year period, FDA is precluded from approving a drug for treatment of the same use or indication. When the designation was granted, no sNDA had been submitted nor had safety and efficacy studies been conducted in any population group.

12. Following the conclusion of clinical trials studying the safety and efficacy of the use of Abilify in the pediatric population with Tourette's Disorder, Otsuka submitted a sNDA to FDA dated February 12, 2014. Ex. C (cover letter). Otsuka's sNDA sought approval for the new indication of the treatment of Tourette's Disorder in pediatric patients – pediatric patients being the only population group in which Otsuka had conducted safety and efficacy studies.

13. Otsuka's application was based on two trials in pediatric patients (ages 6-18) with Tourette's Disorder. Otsuka recognized that, although symptoms of Tourette's Disorder "can occur in patients as young as 2 years old, with patients having a mean age at onset of 7 years," "[b]ased upon the current labeling," the safety and efficacy of the only FDA-approved drugs for the treatment of Tourette's Disorder had not been "confirmed in patients younger than 12 years of age." Otsuka recognized, "There is a clear unmet medical need in younger patients because the symptoms of TD can manifest at a very early age, and there are no well-controlled trials confirming the safety and efficacy of the currently approved medications in these younger patients. The currently approved typical antipsychotics have a poor tolerability profile and side effects that affect compliance." As a result, Otsuka devised trials "to investigate the safety and efficacy of aripiprazole in this indication [*i.e.*, pediatric patients (aged 6-17 years)]."

14. Otsuka conducted two phase 3, double-blind, placebo-controlled trials in the pediatric population from 6 years of age to 18 years of age. The first trial was an 8-week multicenter, randomized, double-blind, placebo-controlled trial that evaluated the safety and efficacy of fixed-dose once-daily aripiprazole in 133 pediatric subjects with Tourette's Disorder ranging from 7 years of age to 17 years of age. The second was a 10-week multicenter, randomized, double-blind placebo-controlled, flexible-dose trial conducted in 61 pediatric subjects ranging from ages 6 years of age to 18 years of age with Tourette's Disorder or chronic tic disorders. Otsuka is also conducting 1 open-label, long-term safety trial in pediatric subjects (7-17 years old). These were the only studies submitted to FDA in support of Otsuka's sNDA.

15. These studies demonstrated that aripiprazole is safe and effective in the treatment of Tourette's Disorder in pediatric patients as demonstrated by a reduction in the total tic score of the Yale Global Tic Severity Scale. A tic is a sudden, rapid, recurrent, nonrhythmic, stereotypic motor movement or vocalization.

16. In its sNDA, based on the results of the clinical trials, Otsuka only recommended dosages for its label based on weights of the pediatric population – those less than 50 kilograms (110 pounds) and those greater or equal to 50 kilograms – and sought approval for the additional indication of the treatment of Tourette's Disorder in pediatric patients.

17. Through the course of developing the clinical trials to support its sNDA (beginning in 2012 with Otsuka's submission of an Investigational New Drug Application to study the drug in the treatment of Tourette's Disorder in the pediatric population), FDA never objected to the pediatric age groups that were the subjects of Otsuka's clinical trials. Rather, FDA's recommendations were instrumental in the design of one of the two pivotal studies described above, including the selection of doses to be evaluated.

18. FDA never objected to Otsuka's seeking an indication limited to the pediatric population and, indeed, acknowledged in comments prior to Otsuka's submission of its sNDA that Otsuka was developing Abilify for the treatment of Tourette's Disorder in children and adolescents.

19. Otsuka engaged in conversations with FDA after submitting its sNDA to substantially revise and "streamline" its label. During those discussions, Otsuka never agreed to broaden its indication beyond the pediatric population, and Otsuka never understood FDA as seeking to broaden the indication beyond the pediatric population.

FDA's Actions

20. On December 12, 2014, FDA sent a letter to Otsuka notifying Otsuka that FDA was granting marketing approval for Abilify "based upon two adequate and well-controlled trials that demonstrate the efficacy for the new indication in pediatric patients with Tourette's Disorder." Ex. D. This approval resulted in substantial modifications to the Abilify label. *Id.*

21. On January 13, 2015, FDA's Office of Orphan Products Development database was updated to reflect that Abilify had been "approved for orphan indication" of "treatment of pediatric patients with Tourette's disorder."

22. Counsel for Otsuka thereafter wrote to FDA's Chief Counsel setting forth Otsuka's position that FDA's approval of Otsuka's sNDA for the use of Abilify in the treatment of Tourette's Disorder *in pediatric patients*, an approval protected by orphan drug exclusivity, precluded FDA from approving an ANDA for a generic version of Abilify pending the expiration of Otsuka's statutory seven-year period of orphan drug market exclusivity for the new indication. Ex. E.

23. On February 24, 2015, FDA sent Otsuka a letter in which the agency informed Otsuka that "as the first sponsor of this drug [aripiprazole] to obtain marketing approval for this indication, [Otsuka] is entitled to seven years of orphan-drug exclusive approval . . . for ***treatment of Tourette's disorder***." Ex. F. That same day, FDA sent Otsuka a "corrected" approval letter, in which FDA advised that its earlier December 12, 2014, approval letter "contained an error in the 'indications' sentence." FDA purported to broaden the approved indication from treatment "in pediatric patients with Tourette's Disorder" to treatment "in patients with Tourette's Disorder." Ex. A.

24. Otsuka did not request this broader indication nor did Otsuka provide adequate and well-controlled studies in its sNDA proving that Abilify is safe and effective for use in the treatment of Tourette's Disorder in the non-pediatric population at large.

25. Otsuka sought clarification of FDA's position on the scope of this revised approval. On March 9, 2015, Otsuka emailed FDA and posed the following direct question: "[D]oes [FDA] consider the supplemental approval to be for the treatment of Tourette's disorder in the general population, or is the approval limited to the pediatric population in which Otsuka demonstrated safety and efficacy?" Ex. G. FDA responded unambiguously on March 11, 2015: "We consider the supplemental approval to be for the treatment of Tourette's disorder in the general population." *Id.*

26. On March 18, 2015, Otsuka emailed FDA and formally objected to FDA's reversal of decision and broadening of the indication. *Id.* Otsuka requested that the broadened indication be rescinded. Otsuka noted that the initial pediatric indication was supported by clinical trial data while the broadened "in the general population" indication was not. Otsuka supported its objection with a declaration from Dr. Floyd Sallee, a Professor of Psychiatry at the

University of Cincinnati School of Medicine who originally requested orphan drug designation. Ex. H. Dr. Sallee has many years of experience treating patients with Tourette's Disorder, both children and adults. *Id.* ¶ 3. Dr. Sallee's declaration addresses the sharp differences in Tourette's Disorder in adults as compared to children and the differences in treatment for the two groups. *Id.* ¶¶ 6-7.

27. Only after FDA was advised of the direct legal consequence of its pediatric approval did FDA reverse course and, without Otsuka's submitting any additional clinical trial information, purport to "strip away" the previously granted pediatric indication. *See* Ex. A.

28. Otsuka received three-year exclusivity under 21 U.S.C. § 355(j)(5)(F)(iv) for "a change approved in the supplement."

Abilify's Currently Approved Label

29. FDA has approved Abilify's labeling, including, as required, information about matters such as dosage and administration and adverse reactions, to accompany the drug with the "corrected" indication of treatment of Tourette's Disorder in the population at large. Given that the only safety and effectiveness data submitted related to the pediatric use of the drug, not the population at large, the label is replete with multiple and extensive references to pediatric use.

30. In the "Highlights of Prescribing Information," for example, the "Indications and Usage" section includes a reference to the clinical trials supporting the new indication supporting the new indication ("Treatment of Tourette's disorder (14.5)"); the "Dosage and Administration" section for Tourette's Disorder is specifically titled for "Pediatric Patients (6 to 18 years)" and lists dosages for pediatric patients less than and greater or equal to 50 kilograms and references the dosage and administration section of the full prescribing information; and the "Adverse

Reactions" section specifically lists adverse reactions for pediatric patients (6 to 18 years old). Ex. A.

31. There are also many references in the "Full Prescribing Information" to pediatric information. These references include the sections related to indications and usage which reference the Tourette's Disorder clinical trials (§ 1); dosage and administration for "pediatric patients (6 to 18 years)" (§ 2.5); warnings and precautions (§ 5.6; text following Table 7 and Table 8); adverse reactions (§ 6.1 Tables 21, 22 and related text); pediatric use (§ 8.4); clinical studies (§§ 14, 14.5 (Tourette's Disorder – Pediatric Patients)).

I declare under penalty of perjury that the foregoing is true and correct.

Executed on the 24th day of March, 2015.

Robert D. McQuade, Ph.D.

Exhibit List

Exhibits	Description
A	Feb. 24, 2015 "Corrected" Approval Letter
B	June 15, 2005 Application for Orphan Drug Designation
C	sNDA Cover Letter
D	December 12, 2014 Original Approval Letter
E	January 21, 2015 Letter from R. Tyler to L. Dickinson
F	ODE Letter to Otsuka
G	March 9, 2015 Email String
H	Dr. Floyd Sallee Declaration

EXHIBIT A

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21436/S-038
NDA 21713/S-030
NDA 21729/S-022
NDA 21866/S-023

SUPPLEMENT APPROVAL

Otsuka Pharmaceutical Development & Commercialization, Inc.
Attention: David Goldberger, RPh, RAC
Vice President, Global Regulatory Affairs
2440 Research Blvd.
Rockville, MD 20850

Dear Mr. Goldberger:

Please refer to your Supplemental New Drug Applications (sNDA) dated and received February 12, 2014 (NDA 21436/S-038), and April 3, 2014 (NDAs 21713/S-030, 21729/S-022, 21866/S-023), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Abilify (aripiprazole) tablets 2 mg, 5 mg, 10 mg, 15 mg, 20 mg, 30 mg (NDA 21436), oral solution 1 mg/ml (NDA 21713), orally disintegrating tablet 10 mg, 15 mg (NDA 21729), and injectable formulation 9.75 mg/1.3 mL single-dose vial (NDA 21866).

We acknowledge receipt of your amendments dated March 7, 2014; March 26, 2014; April 30, 2014; June 10, 2014; June 20, 2014; June 26, 2014; August 29, 2014; October 28, 2014; November 14, 2014; November 24, 2014; December 2, 2014, December 8, 2014, and December 9, 2014.

Please also refer to our approval letter dated December 12, 2014. That letter contained an error in the "indications" sentence as described below:

Prior Statement: "These 'Prior Approval' supplemental new drug applications provide for labeling revisions based upon two adequate and well-controlled trials that demonstrate the efficacy for the new indication in pediatric patients with Tourette's Disorder."

Corrected Statement: "These 'Prior Approval' supplemental new drug applications provide for labeling revisions based upon two adequate and well-controlled trials that demonstrate the efficacy for the new indication in patients with Tourette's Disorder."

The effective approval date will remain December 12, 2014, the date of the original approval letter. The corrected labeling is unchanged.

APPROVAL & LABELING

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

WAIVER OF HIGHLIGHTS SECTION

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

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.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment agreed upon in your communication dated November 14, 2014:

2837-1 A controlled trial to evaluate the longer-term (i.e., maintenance) efficacy of aripiprazole in the treatment of pediatric patients (6-17 years) Tourette's Disorder. This trial must include a placebo group and more than one fixed dose and must utilize a randomized withdrawal design, following an adequate period of stabilization with open-label treatment of aripiprazole. Because it is important to establish the dose-response for maintenance, this trial should randomize patients on stable doses of aripiprazole and different doses of aripiprazole (and to placebo) during the maintenance phase.

The timetable you submitted on November 25, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 01/31/2016
Trial Completion: 07/31/2021
Final Report Submission: 07/31/2022

Submit clinical protocols to your IND 116003 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to this postmarketing commitment should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

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, please call CAPT William Bender, Senior Regulatory Project Manager, at (301) 796-2145 or via email at william.bender@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Mitchell V. Mathis, M.D.
CAPT, USPHS
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:
Content of 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

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS and SUICIDAL THOUGHTS AND BEHAVIORS WITH 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)
- Increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants. Monitor for worsening and emergence of suicidal thoughts and behaviors. (5.2)

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

Indication, Treatment of Tourette's Disorder (1)	12/2014
Dosage and Administration, Tourette's Disorder (2.5)	12/2014
Warnings and Precautions, Metabolic Changes (5.6)	12/2014

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

ABILIFY is an atypical antipsychotic. The oral formulations are indicated for:

- Schizophrenia (14.1)
- Acute Treatment of Manic and Mixed Episodes associated with Bipolar I (14.2)
- Adjunctive Treatment of Major Depressive Disorder (14.3)
- Irritability Associated with Autistic Disorder (14.4)
- Treatment of Tourette's disorder (14.5)

The injection is indicated for:

- Agitation associated with schizophrenia or bipolar mania (14.6)

---------- 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 (2.2)		15 mg/day	15 mg/day	30 mg/day
Bipolar mania – adults: adjunct to lithium or valproate (2.2)		10-15 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
Major Depressive Disorder – Adults adjunct to antidepressants (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
Tourette's disorder – (2.5)	Patients < 50 kg	2 mg/day	5 mg/day	10 mg/day
	Patients ≥ 50 kg	2 mg/day	10 mg/day	20 mg/day
Agitation associated with schizophrenia or bipolar mania – adults (2.6)		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)
- Known CYP2D6 poor metabolizers: Half of the usual dose (2.7)

---------- 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 ----------

- *Cerebrovascular Adverse Reactions in Elderly Patients with Dementia-Related Psychosis:* Increased incidence of cerebrovascular adverse reactions (e.g., stroke, transient ischemic attack, including fatalities) (5.2)
- *Neuroleptic Malignant Syndrome:* Manage with immediate discontinuation and close monitoring (5.3)
- *Tardive Dyskinesia:* Discontinue if clinically appropriate (5.4)
- *Metabolic Changes:* Atypical antipsychotic drugs have been associated with metabolic changes that include hyperglycemia/diabetes mellitus, dyslipidemia, and body weight gain (5.5)
  - *Hyperglycemia/Diabetes Mellitus:* Monitor glucose regularly in patients with and at risk for diabetes (5.5)
  - *Dyslipidemia:* Undesirable alterations in lipid levels have been observed in patients treated with atypical antipsychotics (5.5)
  - *Weight Gain:* Weight gain has been observed with atypical antipsychotic use. Monitor weight (5.5)
- *Orthostatic Hypotension:* Monitor heart rate and blood pressure and warn patients with known cardiovascular or cerebrovascular disease, and risk of dehydration or syncope (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 (6.1):

- 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
- Pediatric patients (6 to 18 years) with Tourette's disorder: sedation, somnolence, nausea, headache, nasopharyngitis, fatigue, increased appetite
- 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.

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

Dosage adjustment due to drug interactions (7.1):

Factors	**Dosage Adjustments for ABILIFY**
Known CYP2D6 Poor Metabolizers	Administer half of usual dose
Known CYP2D6 Poor Metabolizers and strong CYP3A4 inhibitors	Administer a quarter of usual dose
Strong CYP2D6 **or** CYP3A4 inhibitors	Administer half of usual dose
Strong CYP2D6 **and** CYP3A4 inhibitors	Administer a quarter of usual dose
Strong CYP3A4 inducers	Double usual dose over 1 to 2 weeks

---------- USE IN SPECIFIC POPULATIONS ----------

- *Pregnancy:* May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure (8.1)
- *Nursing Mothers:* Discontinue drug or nursing, taking into consideration importance of drug to the mother (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 12/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS and SUICIDAL THOUGHTS AND BEHAVIORS WITH ANTIDEPRESSANT DRUGS

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 *[see Warnings and Precautions (5.1)]*.

Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term studies. These studies did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in patients over age 24; there was a reduction in risk with antidepressant use in patients aged 65 and older *[see Warnings and Precautions (5.2)]*.

In patients of all ages who are started on antidepressant therapy, monitor closely for worsening, and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber *[see Warnings and Precautions (5.2)]*.

1 INDICATIONS AND USAGE

ABILIFY Oral Tablets, Orally-Disintegrating Tablets, and Oral Solution are indicated for the treatment of:

- Schizophrenia *[see CLINICAL STUDIES (14.1)]*
- Acute Treatment of Manic and Mixed Episodes associated with Bipolar I Disorder *[see CLINICAL STUDIES (14.2)]*
- Adjunctive Treatment of Major Depressive Disorder *[see CLINICAL STUDIES (14.3)]*
- Irritability Associated with Autistic Disorder *[see CLINICAL STUDIES (14.4)]*
- Treatment of Tourette's Disorder *[see CLINICAL STUDIES (14.5)]*

ABILIFY Injection is indicated for the treatment of:

- Agitation associated with schizophrenia or bipolar mania *[see CLINICAL STUDIES (14.6)]*

2 DOSAGE AND ADMINISTRATION

2.1 Schizophrenia

Adults

The recommended starting and target dose for ABILIFY is 10 or 15 mg/day administered on a once-a-day schedule without regard to meals. ABILIFY has been systematically evaluated and shown to be effective in a dose range of 10 to 30 mg/day, when administered as the tablet formulation; however, doses higher than 10 or 15 mg/day were not more effective than 10 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

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)]*. 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

Acute Treatment of Manic and Mixed Episodes

Adults: The recommended starting dose in adults is 15 mg given once daily as monotherapy and 10 mg to 15 mg given once daily as adjunctive therapy with lithium or valproate. ABILIFY can be given without regard to meals. The recommended target dose of ABILIFY is 15 mg/day, as monotherapy or as adjunctive therapy with lithium or valproate. 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.

Pediatrics: The recommended starting dose in pediatric patients (10 to 17 years) as monotherapy is 2 mg/day, with titration to 5 mg/day after 2 days, and a target dose of 10 mg/day after 2 additional days. Recommended dosing as adjunctive therapy to lithium or valproate is the same. Subsequent dose increases, if needed, should be administered in 5 mg/day increments. ABILIFY can be given without regard to meals *[see CLINICAL STUDIES (14.2)]*.

2.3 Adjunctive Treatment of Major Depressive Disorder

Adults

The recommended starting dose for ABILIFY as adjunctive treatment for patients already taking an antidepressant is 2 to 5 mg/day. The recommended dosage range is 2 to 15 mg/day. Dosage adjustments of up to 5 mg/day should occur gradually, at intervals of no less than 1 week *[see CLINICAL STUDIES (14.3)]*. Patients should be periodically reassessed to determine the continued need for maintenance treatment.

2.4 Irritability Associated with Autistic Disorder

Pediatric Patients (6 to 17 years)

The recommended dosage range for the treatment of pediatric patients with irritability associated with autistic disorder is 5 to 15 mg/day.

Dosing should be initiated at 2 mg/day. The dose should be increased to 5 mg/day, with subsequent increases to 10 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)]*. Patients should be periodically reassessed to determine the continued need for maintenance treatment.

2.5 Tourette's Disorder

Pediatric Patients (6 to 18 years)

The recommended dosage range for Tourette's Disorder is 5 to 20 mg/day.

For patients weighing less than 50 kg, dosing should be initiated at 2 mg/day with a target dose of 5 mg/day after 2 days. The dose can be increased to 10 mg/day in patients who do not achieve optimal control of tics. Dosage adjustments should occur gradually at intervals of no less than 1 week.

For patients weighing 50 kg or more, dosing should be initiated at 2 mg/day for 2 days, and then increased to 5 mg/day for 5 days, with a target dose of 10 mg/day on day 8. The dose can be increased up to 20 mg/day for patients who do not achieve optimal control of tics. Dosage adjustments should occur gradually in increments of 5 mg/day at intervals of no less than 1 week. *[see CLINICAL STUDIES (14.5)]*.

Patients should be periodically reassessed to determine the continued need for maintenance treatment.

2.6 Agitation Associated with Schizophrenia or Bipolar Mania (Intramuscular Injection)

Adults

The recommended dose in these patients is 9.75 mg. The recommended dosage range is 5.25 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 ABILIFY 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. 6)]*.

If ongoing ABILIFY therapy is clinically indicated, oral ABILIFY in a range of 10 to 30 mg/day should replace ABILIFY 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.

2.7 Dosage Adjustments for Cytochrome P450 Considerations

Dosage adjustments are recommended in patients who are known CYP2D6 poor metabolizers and in patients taking concomitant CYP3A4 inhibitors or CYP2D6 inhibitors or strong CYP3A4 inducers (see Table 2). When the coadministered drug is withdrawn from the combination therapy, ABILIFY dosage should then be adjusted to its original level. When the coadministered CYP3A4 inducer is withdrawn, ABILIFY dosage should be reduced to the original level over 1 to 2 weeks. Patients who may be receiving a combination of strong, moderate, and weak inhibitors of CYP3A4 and CYP2D6 (e.g., a strong CYP3A4 inhibitor and a moderate CYP2D6 inhibitor or a moderate CYP3A4 inhibitor with a moderate CYP2D6 inhibitor), the dosing may be reduced to one-quarter (25%) of the usual dose initially and then adjusted to achieve a favorable clinical response.

Table 2: Dose Adjustments for ABILIFY in Patients who are known CYP2D6 Poor Metabolizers and Patients Taking Concomitant CYP2D6 Inhibitors, 3A4 Inhibitors, and/or CYP3A4 Inducers

Factors	**Dosage Adjustments for ABILIFY**
Known CYP2D6 Poor Metabolizers	Administer half of usual dose
Known CYP2D6 Poor Metabolizers taking concomitant strong CYP3A4 inhibitors (e.g., itraconazole, clarithromycin)	Administer a quarter of usual dose
Strong CYP2D6 (e.g., quinidine, fluoxetine, paroxetine) **or** CYP3A4 inhibitors (e.g., itraconazole, clarithromycin)	Administer half of usual dose
Strong CYP2D6 **and** CYP3A4 inhibitors	Administer a quarter of usual dose
Strong CYP3A4 inducers (e.g., carbamazepine, rifampin)	Double usual dose over 1 to 2 weeks

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)*.

2.8 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)]*.

2.9 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® (aripiprazole) Tablets are available as described in Table 3.

Table 3: ABILIFY Tablet Presentations

Tablet Strength	Tablet Color/Shape	Tablet Markings
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® (aripiprazole) Orally Disintegrating Tablets are available as described in Table 4.

Table 4: ABILIFY DISCMELT Orally Disintegrating Tablet Presentations

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

ABILIFY® (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® (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

ABILIFY is contraindicated in patients with a history of a hypersensitivity reaction to aripiprazole. Reactions have ranged from pruritus/urticaria to anaphylaxis *[see ADVERSE REACTIONS (6.2)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Increased Mortality 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]*.

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

In three, 10-week, placebo-controlled studies of ABILIFY in elderly patients with psychosis associated with Alzheimer's disease (n=938; mean age: 82.4 years; range: 56-99 years), the adverse reactions that were reported at an incidence of ≥3% and ABILIFY incidence at least twice that for placebo were lethargy [placebo 2%, ABILIFY 5%], somnolence (including sedation) [placebo 3%, ABILIFY 8%], and incontinence (primarily, urinary incontinence) [placebo 1%, ABILIFY 5%], excessive salivation [placebo 0%, ABILIFY 4%], and lightheadedness [placebo 1%, ABILIFY 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, assess for the emergence of difficulty swallowing or excessive somnolence, which could predispose to accidental injury or aspiration *[see also BOXED WARNING]*.

5.2 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 (e.g., stroke, transient ischemic attack), including fatalities, in ABILIFY-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 ABILIFY. ABILIFY is not approved for the treatment of patients with dementia-related psychosis *[see also BOXED WARNING]*.

5.3 Suicidal Thoughts and Behaviors in Children, Adolescents, and Young Adults

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 5.

Table 5:

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated
	Increases Compared to Placebo
<18	14 additional cases
18-24	5 additional cases
	Decreases Compared to Placebo
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.

5.4 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 ABILIFY. Rare cases of NMS occurred during ABILIFY 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 (e.g., 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.

5.5 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.

5.6 Metabolic Changes

Atypical antipsychotic drugs have been associated with metabolic changes that include hyperglycemia/diabetes mellitus, dyslipidemia, and body weight gain. While all drugs in the class have been shown to produce some metabolic changes, each drug has its own specific risk profile.

Hyperglycemia/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 reports of hyperglycemia in patients treated with ABILIFY *[see ADVERSE REACTIONS (6.1, 6.2)]*. 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 suggest an increased risk of hyperglycemia-related adverse reactions in patients treated with the atypical antipsychotics. 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 reactions 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 (e.g., 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.

Adults

In an analysis of 13 placebo-controlled monotherapy trials in adults, primarily with schizophrenia or bipolar disorder, the mean change in fasting glucose in ABILIFY-treated patients (+4.4 mg/dL; median exposure 25 days; N=1057) was not significantly different than in placebo-treated patients (+2.5 mg/dL; median exposure 22 days; N=799). Table 6 shows the proportion of ABILIFY-treated patients with normal and borderline fasting glucose at baseline (median exposure 25 days) that had treatment-emergent high fasting glucose measurements compared to placebo-treated patients (median exposure 22 days).

Table 6: Changes in Fasting Glucose From Placebo-Controlled Monotherapy Trials in Adult Patients

	Category Change (at least once) from Baseline	Treatment Arm	n/N	%
Fasting Glucose	Normal to High (<100 mg/dL to ≥126 mg/dL)	ABILIFY	31/822	3.8
		Placebo	22/605	3.6
	Borderline to High (≥100 mg/dL and <126 mg/dL to ≥126 mg/dL)	ABILIFY	31/176	17.6
		Placebo	13/142	9.2

At 24 weeks, the mean change in fasting glucose in ABILIFY-treated patients was not significantly different than in placebo-treated patients [+2.2 mg/dL (n=42) and +9.6 mg/dL (n=28), respectively].

The mean change in fasting glucose in adjunctive ABILIFY-treated patients with major depressive disorder (+0.7 mg/dL; median exposure 42 days; N=241) was not significantly different than in placebo-treated patients (+0.8 mg/dL; median exposure 42 days; N=246). Table 7 shows the proportion of adult patients with changes in fasting glucose levels from two placebo-controlled, adjunctive trials (median exposure 42 days) in patients with major depressive disorder.

Table 7: Changes in Fasting Glucose From Placebo-Controlled Adjunctive Trials in Adult Patients with Major Depressive Disorder

	Category Change (at least once) from Baseline	Treatment Arm	n/N	%
Fasting Glucose	Normal to High (<100 mg/dL to ≥126 mg/dL)	ABILIFY	2/201	1.0
		Placebo	2/204	1.0
	Borderline to High (≥100 mg/dL and <126 mg/dL to ≥126 mg/dL)	ABILIFY	4/34	11.8
		Placebo	3/37	8.1

Pediatric Patients and Adolescents

In an analysis of two placebo-controlled trials in adolescents with schizophrenia (13 to 17 years) and pediatric patients with bipolar disorder (10 to 17 years), the mean change in fasting glucose in ABILIFY-treated patients (+4.8 mg/dL; with a median exposure of 43 days; N=259) was not significantly different than in placebo-treated patients (+1.7 mg/dL; with a median exposure of 42 days; N=123).

In an analysis of two placebo-controlled trials in pediatric and adolescent patients with irritability associated with autistic disorder (6 to 17 years) with median exposure of 56 days, the mean change in fasting glucose in ABILIFY-treated patients (–0.2 mg/dL; N=83) was not significantly different than in placebo-treated patients (–0.6 mg/dL; N=33).

In an analysis of two placebo-controlled trials in pediatric and adolescent patients with Tourette's disorder (6 to 18 years) with median exposure of 57 days, the mean change in fasting glucose in ABILIFY-treated patients (0.79 mg/dL; N=90) was not significantly different than in placebo-treated patients (–1.66 mg/dL; N=58).

Table 8 shows the proportion of patients with changes in fasting glucose levels from the pooled adolescent schizophrenia and pediatric bipolar patients (median exposure of 42-43 days), from two placebo-controlled trials in pediatric patients (6 to 17 years) with irritability associated with autistic disorder (median exposure of 56 days), and from the two placebo-controlled trials in pediatric patients (6 to 18 year) with Tourette's Disorder (median exposure 57 days).

Table 8: Changes in Fasting Glucose From Placebo-Controlled Trials in Pediatric and Adolescent Patients

Category Change (at least once) from Baseline	Indication	Treatment Arm	n/N	%
Fasting Glucose Normal to High (<100 mg/dL to ≥126 mg/dL)	Pooled Schizophrenia and Bipolar Disorder	ABILIFY	2/236	0.8
		Placebo	2/110	1.8
	Irritability Associated with Autistic Disorder	ABILIFY	0/73	0
		Placebo	0/32	0
	Tourette's Disorder	ABILIFY	3/88	3.4
		Placebo	1/58	1.7
Fasting Glucose Borderline to High (≥100 mg/dL and <126 mg/dL to ≥126 mg/dL)	Pooled Schizophrenia and Bipolar Disorder	ABILIFY	1/22	4.5
		Placebo	0/12	0
	Irritability Associated with Autistic Disorder	ABILIFY	0/9	0
		Placebo	0/1	0
	Tourette's Disorder	ABILIFY	0/11	0
		Placebo	0/4	0

At 12 weeks in the pooled adolescent schizophrenia and pediatric bipolar disorder trials, the mean change in fasting glucose in ABILIFY-treated patients was not significantly different than in placebo-treated patients [+2.4 mg/dL (n=81) and +0.1 mg/dL (n=15), respectively].

Dyslipidemia

Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.

There were no significant differences between ABILIFY- and placebo-treated patients in the proportion with changes from normal to clinically significant levels for fasting/nonfasting total cholesterol, fasting triglycerides, fasting LDLs, and

fasting/nonfasting HDLs. Analyses of patients with at least 12 or 24 weeks of exposure were limited by small numbers of patients.

Adults

Table 9 shows the proportion of adult patients, primarily from pooled schizophrenia and bipolar disorder monotherapy placebo-controlled trials, with changes in total cholesterol (pooled from 17 trials; median exposure 21 to 25 days), fasting triglycerides (pooled from eight trials; median exposure 42 days), fasting LDL cholesterol (pooled from eight trials; median exposure 39 to 45 days, except for placebo-treated patients with baseline normal fasting LDL measurements, who had median treatment exposure of 24 days) and HDL cholesterol (pooled from nine trials; median exposure 40 to 42 days).

Table 9: Changes in Blood Lipid Parameters From Placebo-Controlled Monotherapy Trials in Adults

	Treatment Arm	n/N	%
Total Cholesterol Normal to High (<200 mg/dL to ≥240 mg/dL)	ABILIFY	34/1357	2.5
	Placebo	27/973	2.8
Fasting Triglycerides Normal to High (<150 mg/dL to ≥200 mg/dL)	ABILIFY	40/539	7.4
	Placebo	30/431	7.0
Fasting LDL Cholesterol Normal to High (<100 mg/dL to ≥160 mg/dL)	ABILIFY	2/332	0.6
	Placebo	2/268	0.7
HDL Cholesterol Normal to Low (≥40 mg/dL to <40 mg/dL)	ABILIFY	121/1066	11.4
	Placebo	99/794	12.5

In monotherapy trials in adults, the proportion of patients at 12 weeks and 24 weeks with changes from Normal to High in total cholesterol (fasting/nonfasting), fasting triglycerides, and fasting LDL cholesterol were similar between ABILIFY- and placebo-treated patients: at 12 weeks, Total Cholesterol (fasting/nonfasting), 1/71 (1.4%) vs. 3/74 (4.1%); Fasting Triglycerides, 8/62 (12.9%) vs. 5/37 (13.5%); Fasting LDL Cholesterol, 0/34 (0%) vs. 1/25 (4.0%), respectively; and at 24 weeks, Total Cholesterol (fasting/nonfasting), 1/42 (2.4%) vs. 3/37 (8.1%); Fasting Triglycerides, 5/34 (14.7%) vs. 5/20 (25%); Fasting LDL Cholesterol, 0/22 (0%) vs. 1/18 (5.6%), respectively.

Table 10 shows the proportion of patients with changes in total cholesterol (fasting/nonfasting), fasting triglycerides, fasting LDL cholesterol, and HDL cholesterol from two placebo-controlled adjunctive trials in adult patients with major depressive disorder (median exposure 42 days).

Table 10: Changes in Blood Lipid Parameters From Placebo-Controlled Adjunctive Trials in Adult Patients with Major Depressive Disorder

	Treatment Arm	n/N	%
Total Cholesterol Normal to High (<200 mg/dL to ≥240 mg/dL)	ABILIFY	3/139	2.2
	Placebo	7/135	5.2
Fasting Triglycerides Normal to High (<150 mg/dL to ≥200 mg/dL)	ABILIFY	14/145	9.7
	Placebo	6/147	4.1
Fasting LDL Cholesterol Normal to High (<100 mg/dL to ≥160 mg/dL)	ABILIFY	0/54	0
	Placebo	0/73	0
HDL Cholesterol Normal to Low (≥40 mg/dL to <40 mg/dL)	ABILIFY	17/318	5.3
	Placebo	10/286	3.5

Pediatric Patients and Adolescents

Table 11 shows the proportion of adolescents with schizophrenia (13 to 17 years) and pediatric patients with bipolar disorder (10 to 17 years) with changes in total cholesterol and HDL cholesterol (pooled from two placebo-controlled trials; median exposure 42 to 43 days) and fasting triglycerides (pooled from two placebo-controlled trials; median exposure 42 to 44 days).

Table 11: Changes in Blood Lipid Parameters From Placebo-Controlled Monotherapy Trials in Pediatric and Adolescent Patients in Schizophrenia and Bipolar Disorder

	Treatment Arm	n/N	%
Total Cholesterol Normal to High (<170 mg/dL to ≥200 mg/dL)	ABILIFY	3/220	1.4
	Placebo	0/116	0
Fasting Triglycerides Normal to High (<150 mg/dL to ≥200 mg/dL)	ABILIFY	7/187	3.7
	Placebo	4/85	4.7
HDL Cholesterol Normal to Low (≥40 mg/dL to <40 mg/dL)	ABILIFY	27/236	11.4
	Placebo	22/109	20.2

In monotherapy trials of adolescents with schizophrenia and pediatric patients with bipolar disorder, the proportion of patients at 12 weeks and 24 weeks with changes from Normal to High in total cholesterol (fasting/nonfasting), fasting triglycerides, and fasting LDL cholesterol were similar between ABILIFY- and placebo-treated patients: at 12 weeks, Total Cholesterol (fasting/nonfasting), 0/57 (0%) vs. 0/15 (0%); Fasting Triglycerides, 2/72 (2.8%) vs. 1/14 (7.1%), respectively; and at 24 weeks, Total

Cholesterol (fasting/nonfasting), 0/36 (0%) vs. 0/12 (0%); Fasting Triglycerides, 1/47 (2.1%) vs. 1/10 (10.0%), respectively.

Table 12 shows the proportion of patients with changes in total cholesterol (fasting/nonfasting) and fasting triglycerides (median exposure 56 days) and HDL cholesterol (median exposure 55 to 56 days) from two placebo-controlled trials in pediatric patients (6 to 17 years) with irritability associated with autistic disorder.

Table 12: Changes in Blood Lipid Parameters From Placebo-Controlled Trials in Pediatric Patients with Autistic Disorder

	Treatment Arm	n/N	%
Total Cholesterol Normal to High (<170 mg/dL to ≥200 mg/dL)	ABILIFY	1/95	1.1
	Placebo	0/34	0
Fasting Triglycerides Normal to High (<150 mg/dL to ≥200 mg/dL)	ABILIFY	0/75	0
	Placebo	0/30	0
HDL Cholesterol Normal to Low (≥40 mg/dL to <40 mg/dL)	ABILIFY	9/107	8.4
	Placebo	5/49	10.2

Table 13 shows the proportion of patients with changes in total cholesterol (fasting/nonfasting) and fasting triglycerides (median exposure 57 days) and HDL cholesterol (median exposure 57 days) from two placebo-controlled trials in pediatric patients (6 to 18 years) with Tourette's Disorder.

Table 13: Changes in Blood Lipid Parameters From Placebo-Controlled Trials in Pediatric Patients with Tourette's Disorder

	Treatment Arm	n/N	%
Total Cholesterol Normal to High (<170 mg/dL to ≥200 mg/dL)	ABILIFY	1/85	1.2
	Placebo	0/46	0
Fasting Triglycerides Normal to High (<150 mg/dL to ≥200 mg/dL)	ABILIFY	5/94	5.3
	Placebo	2/55	3.6
HDL Cholesterol Normal to Low (≥40 mg/dL to <40 mg/dL)	ABILIFY	4/108	3.7
	Placebo	2/67	3.0

Weight Gain

Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

Adults

In an analysis of 13 placebo-controlled monotherapy trials, primarily from pooled schizophrenia and bipolar disorder, with a median exposure of 21 to 25 days, the mean change in body weight in ABILIFY-treated patients was +0.3 kg (N=1673) compared to –0.1 kg (N=1100) in placebo-controlled patients. At 24 weeks, the mean change from baseline in body weight in ABILIFY-treated patients was –1.5 kg (n=73) compared to –0.2 kg (n=46) in placebo-treated patients.

In the trials adding ABILIFY to antidepressants, patients first received 8 weeks of antidepressant treatment followed by 6 weeks of adjunctive ABILIFY or placebo in addition to their ongoing antidepressant treatment. The mean change in body weight in patients receiving adjunctive ABILIFY was +1.7 kg (N=347) compared to +0.4 kg (N=330) in patients receiving adjunctive placebo.

Table 14 shows the percentage of adult patients with weight gain ≥7% of body weight by indication.

Table 14: Percentage of Patients From Placebo-Controlled Trials in Adult Patients with Weight Gain ≥7% of Body Weight

	Indication	Treatment Arm	N	Patients n (%)
Weight gain ≥7% of body weight	Schizophrenia[a]	ABILIFY	852	69 (8.1)
		Placebo	379	12 (3.2)
	Bipolar Mania[b]	ABILIFY	719	16 (2.2)
		Placebo	598	16 (2.7)
	Major Depressive Disorder (Adjunctive Therapy)[c]	ABILIFY	347	18 (5.2)
		Placebo	330	2 (0.6)

[a] 4-6 weeks duration. [b] 3 weeks duration. [c] 6 weeks duration.

Pediatric Patients and Adolescents

In an analysis of two placebo-controlled trials in adolescents with schizophrenia (13 to 17 years) and pediatric patients with bipolar disorder (10 to 17 years) with median exposure of 42 to 43 days, the mean change in body weight in ABILIFY-treated patients was +1.6 kg (N=381) compared to +0.3 kg (N=187) in placebo-treated patients. At 24 weeks, the mean change from baseline in body weight in ABILIFY-treated patients was +5.8 kg (n=62) compared to +1.4 kg (n=13) in placebo-treated patients.

In two short-term, placebo-controlled trials in patients (6 to 17 years) with irritability associated with autistic disorder with median exposure of 56 days, the mean change in body weight in ABILIFY-treated patients was +1.6 kg (n=209) compared to +0.4 kg (n=98) in placebo-treated patients.

In two short-term, placebo-controlled trials in patients (6 to 18 years) with Tourette's Disorder with median exposure of 57 days, the mean change in body weight in ABILIFY-treated patients was +1.5 kg (n=105) compared to +0.4 kg (n=66) in placebo-treated patients.

Table 15 shows the percentage of pediatric and adolescent patients with weight gain ≥7% of body weight by indication.

Table 15: Percentage of Patients From Placebo-Controlled Monotherapy Trials in Pediatric and Adolescent Patients with Weight Gain ≥7% of Body Weight

	Indication	Treatment Arm	N	Patients n (%)
Weight gain ≥7% of body weight	Pooled Schizophrenia and Bipolar Mania[a]	ABILIFY	381	20 (5.2)
		Placebo	187	3 (1.6)
	Irritability Associated with Autistic Disorder[b]	ABILIFY	209	55 (26.3)
		Placebo	98	7 (7.1)
	Tourette's Disorder[c]	ABILIFY	105	21 (20.0)
		Placebo	66	5 (7.6)

[a] 4-6 weeks duration. [b] 8 weeks duration. [c] 8-10 weeks duration.

In an open-label trial that enrolled patients from the two placebo-controlled trials of adolescents with schizophrenia (13 to 17 years) and pediatric patients with bipolar disorder (10 to 17 years), 73.2% of patients (238/325) completed 26 weeks of therapy with ABILIFY. After 26 weeks, 32.8% of patients gained ≥7% of their body weight, not adjusted for normal growth. To adjust for normal growth, z-scores were derived (measured in standard deviations [SD]), which normalize for the natural growth of pediatric patients and adolescents by comparisons to age- and gender-matched population standards. A z-score change <0.5 SD is considered not clinically significant. After 26 weeks, the mean change in z-score was 0.09 SD.

In an open-label trial that enrolled patients from two short-term, placebo-controlled trials, patients (6 to 17 years) with irritability associated with autistic disorder, as well as *de novo* patients, 60.3% (199/330) completed one year of therapy with ABILIFY. The mean change in weight z-score was 0.26 SDs for patients receiving >9 months of treatment.

When treating pediatric patients for any indication, weight gain should be monitored and assessed against that expected for normal growth.

5.7 Orthostatic Hypotension

ABILIFY may cause orthostatic hypotension, perhaps due to its α_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 (ABILIFY 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 18 years of age (n=732) on oral ABILIFY included orthostatic hypotension (0.5%, 0%), postural dizziness (0.4%, 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%). *[see ADVERSE REACTIONS (6.1)]*

The incidence of a significant orthostatic change in blood pressure (defined as a decrease in systolic blood pressure ≥20 mmHg accompanied by an increase in heart rate ≥25 bpm when comparing standing to supine values) for ABILIFY was not meaningfully different from placebo (ABILIFY incidence, placebo incidence): in adult oral ABILIFY-treated patients (4%, 2%), in pediatric oral ABILIFY-treated patients aged 6 to 18 years (0.4%, 1%), or in ABILIFY injection-treated patients (3%, 2%).

ABILIFY 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) *[see DRUG INTERACTIONS (7.1)]*.

If parenteral benzodiazepine therapy is deemed necessary in addition to ABILIFY injection treatment, patients should be monitored for excessive sedation and for orthostatic hypotension *[see DRUG INTERACTIONS (7.1)*].

5.8 Leukopenia, Neutropenia, and Agranulocytosis

In clinical trials and/or postmarketing experience, events of leukopenia and 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)/absolute neutrophil count (ANC) and history of drug-induced leukopenia/neutropenia. In patients with a history of a clinically significant low WBC/ANC or drug-induced leukopenia/neutropenia, perform a complete blood count (CBC) frequently during the first few months of therapy. In such patients, consider discontinuation of ABILIFY at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Monitor patients with clinically significant neutropenia for fever or other symptoms or signs of infection and treat promptly if such symptoms or signs occur. Discontinue ABILIFY in patients with severe neutropenia (absolute neutrophil count <1000/mm3) and follow their WBC counts until recovery.

5.9 Seizures/Convulsions

In short-term, placebo-controlled trials, patients with a history of seizures excluded seizures/convulsions occurred in 0.1% (3/2467) of undiagnosed adult patients treated with oral ABILIFY, in 0.1% (1/732) of pediatric patients (6 to 18 years), and in 0.2% (1/501) of adult ABILIFY injection-treated patients.

As with other antipsychotic drugs, ABILIFY should be used cautiously in patients with a history of seizures or with conditions that lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

5.10 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 (ABILIFY 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% (20/732) of pediatric patients (6 to 18 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.

5.11 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 ABILIFY for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, (e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration) *[see ADVERSE REACTIONS (6.2)]*.

5.12 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 (6.1, 6.2)]*.

5.13 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. ABILIFY and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia *[see WARNINGS AND PRECAUTIONS (5.1)* and *ADVERSE REACTIONS (6.2)]*.

6 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

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

- Increased Mortality in Elderly Patients with Dementia-Related Psychosis *[see BOXED WARNING and WARNINGS AND PRECAUTIONS (5.1)]*
- Cerebrovascular Adverse Events, Including Stroke *[see WARNINGS AND PRECAUTIONS (5.2)]*
- Suicidal Thoughts and Behaviors in Children, Adolescents, and Young Adults *[see BOXED WARNING and WARNINGS AND PRECAUTIONS (5.3)]*
- Neuroleptic Malignant Syndrome (NMS) *[see WARNINGS AND PRECAUTIONS (5.4)]*
- Tardive Dyskinesia *[see WARNINGS AND PRECAUTIONS (5.5)]*
- Metabolic Changes *[see WARNINGS AND PRECAUTIONS (5.6)]*
- Orthostatic Hypotension *[see WARNINGS AND PRECAUTIONS (5.7)]*
- Leukopenia, Neutropenia, and Agranulocytosis *[see WARNINGS AND PRECAUTIONS (5.8)]*
- Seizures/Convulsions *[see WARNINGS AND PRECAUTIONS (5.9)]*
- Potential for Cognitive and Motor Impairment *[see WARNINGS AND PRECAUTIONS (5.10)]*
- Body Temperature Regulation *[see WARNINGS AND PRECAUTIONS (5.11)]*
- Suicide *[see WARNINGS AND PRECAUTIONS (5.12)]*

- Dysphagia *[see WARNINGS AND PRECAUTIONS (5.13)]*

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

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

ABILIFY 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 ABILIFY and 749 patients with exposure to ABILIFY injection. A total of 3390 patients were treated with oral ABILIFY for at least 180 days and 1933 patients treated with oral ABILIFY had at least 1 year of exposure.

ABILIFY has been evaluated for safety in 1,686 patients (6 to 18 years) who participated in multiple-dose, clinical trials in schizophrenia, bipolar mania, autistic disorder, or Tourette's disorder and who had approximately 1,342 patient-years of exposure to oral ABILIFY. A total of 959 pediatric patients were treated with oral ABILIFY for at least 180 days and 556 pediatric patients treated with oral ABILIFY had at least 1 year of exposure.

The conditions and duration of treatment with ABILIFY (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.

6.1 Clinical Trials 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 ABILIFY was administered in doses ranging from 2 to 30 mg/day.

Commonly Observed Adverse Reactions

The only commonly observed adverse reaction associated with the use of ABILIFY in patients with schizophrenia (incidence of 5% or greater and ABILIFY incidence at least twice that for placebo) was akathisia (ABILIFY 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 ABILIFY was administered at doses of 15 or 30 mg/day.

Commonly Observed Adverse Reactions

Commonly observed adverse reactions associated with the use of ABILIFY in patients with bipolar mania (incidence of 5% or greater and ABILIFY incidence at least twice that for placebo) are shown in Table 16.

Table 16: Commonly Observed Adverse Reactions in Short-Term, Placebo-Controlled Trials of Adult Patients with Bipolar Mania Treated with Oral ABILIFY Monotherapy

	Percentage of Patients Reporting Reaction	
Preferred Term	**ABILIFY (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 17 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 ABILIFY (doses ≥2 mg/day) and for which the incidence in patients treated with ABILIFY was greater than the incidence in patients treated with placebo in the combined dataset.

Table 17: Adverse Reactions in Short-Term, Placebo-Controlled Trials in Adult Patients Treated with Oral ABILIFY

	Percentage of Patients Reporting Reaction[a]	
System Organ Class **Preferred Term**	**ABILIFY (n=1843)**	**Placebo (n=1166)**
Eye Disorders		
Blurred Vision	3	1
Gastrointestinal Disorders		
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
General Disorders and Administration Site Conditions		
Fatigue	6	4
Pain	3	2
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal Stiffness	4	3
Pain in Extremity	4	2
Myalgia	2	1
Muscle Spasms	2	1
Nervous System Disorders		
Headache	27	23
Dizziness	10	7
Akathisia	10	4
Sedation	7	4
Extrapyramidal Disorder	5	3
Tremor	5	3
Somnolence	5	3
Psychiatric Disorders		
Agitation	19	17
Insomnia	18	13
Anxiety	17	13
Restlessness	5	3
Respiratory, Thoracic, and Mediastinal Disorders		
Pharyngolaryngeal Pain	3	2
Cough	3	2

[a] Adverse reactions reported by at least 2% of patients treated with oral ABILIFY, 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 ABILIFY was administered at doses of 15 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 ABILIFY compared to 6% for patients treated with adjunctive placebo. The most common adverse drug reactions associated with discontinuation in the adjunctive ABILIFY-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 ABILIFY 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 18 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 ABILIFY (doses of 15 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 18: Adverse Reactions in a Short-Term, Placebo-Controlled Trial of Adjunctive Therapy in Patients with Bipolar Disorder

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

[a] Adverse reactions reported by at least 2% of patients treated with oral ABILIFY, 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 ABILIFY was administered in doses ranging from 2 to 30 mg/day.

Adverse Reactions Associated with Discontinuation of Treatment

The incidence of discontinuation due to adverse reactions between ABILIFY-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 ABILIFY in adolescent patients with schizophrenia (incidence of 5% or greater and ABILIFY 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 ABILIFY was administered in doses of 10 or 30 mg/day.

Adverse Reactions Associated with Discontinuation of Treatment

The incidence of discontinuation due to adverse reactions between ABILIFY-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 ABILIFY in pediatric patients with bipolar mania (incidence of 5% or greater and ABILIFY incidence at least twice that for placebo) are shown in Table 19.

Table 19: Commonly Observed Adverse Reactions in Short-Term, Placebo-Controlled Trials of Pediatric Patients (10 to 17 years) with Bipolar Mania Treated with Oral ABILIFY

	Percentage of Patients Reporting Reaction	
Preferred Term	**ABILIFY (n=197)**	**Placebo (n=97)**
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 ABILIFY was administered in doses of 2 to 15 mg/day.

Adverse Reactions Associated with Discontinuation of Treatment

The incidence of discontinuation due to adverse reactions between ABILIFY-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 ABILIFY in pediatric patients with autistic disorder (incidence of 5% or greater and ABILIFY incidence at least twice that for placebo) are shown in Table 20.

Table 20: Commonly Observed Adverse Reactions in Short-Term, Placebo-Controlled Trials of Pediatric Patients (6 to 17 years) with Autistic Disorder Treated with Oral ABILIFY

	Percentage of Patients Reporting Reaction	
Preferred Term	**ABILIFY (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

Pediatric Patients (6 to 18 years) with Tourette's Disorder

The following findings are based on one 8-week and one 10-week, placebo-controlled trials in which oral ABILIFY was administered in doses of 2 to 20 mg/day.

Adverse Reactions Associated with Discontinuation of Treatment

The incidence of discontinuation due to adverse reactions between ABILIFY-treated and placebo-treated pediatric patients (6 to 18 years) was 7% and 1%, respectively.

Commonly Observed Adverse Reactions

Commonly observed adverse reactions associated with the use of ABILIFY in pediatric patients with Tourette's disorder (incidence of 5% or greater and ABILIFY incidence at least twice that for placebo) are shown in Table 21.

Table 21: Commonly Observed Adverse Reactions in Short-Term, Placebo-Controlled Trials of Pediatric Patients (6 to 18 years) with Tourette's Disorder Treated with Oral ABILIFY

	Percentage of Patients Reporting Reaction	
Preferred Term	**ABILIFY (n=121)**	**Placebo (n=72)**
Sedation	13	6
Somnolence	13	1
Nausea	11	4
Headache	10	3
Nasopharyngitis	9	0
Fatigue	8	0
Increased Appetite	7	1

Less Common Adverse Reactions in Pediatric Patients (6 to 18 years) with Schizophrenia, Bipolar Mania, Autistic Disorder, or Tourette's Disorder

Table 22 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, up to 8 weeks in autistic disorder, and up to 10 weeks in Tourette's disorder), including only those reactions that occurred in 2% or more of pediatric patients treated with ABILIFY (doses ≥2 mg/day) and for which the incidence in patients treated with ABILIFY was greater than the incidence in patients treated with placebo.

Table 22: Adverse Reactions in Short-Term, Placebo-Controlled Trials of Pediatric Patients (6 to 18 years) Treated with Oral ABILIFY

	Percentage of Patients Reporting Reaction[a]	
System Organ Class **Preferred Term**	**ABILIFY (n=732)**	**Placebo (n=370)**
Eye Disorders		
Blurred Vision	3	0
Gastrointestinal Disorders		
Abdominal Discomfort	2	1
Vomiting	8	7
Nausea	8	4
Diarrhea	4	3
Salivary Hypersecretion	4	1
Abdominal Pain Upper	3	2

Constipation	2	2
General Disorders and Administration Site Conditions		
Fatigue	10	2
Pyrexia	4	1
Irritability	2	1
Asthenia	2	1
Infections and Infestations		
Nasopharyngitis	6	3
Investigations		
Weight Increased	3	1
Metabolism and Nutrition Disorders		
Increased Appetite	7	3
Decreased Appetite	5	4
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal Stiffness	2	1
Muscle Rigidity	2	1
Nervous System Disorders		
Somnolence	16	4
Headache	12	10
Sedation	9	2
Tremor	9	1
Extrapyramidal Disorder	6	1
Akathisia	6	4
Drooling	3	0
Lethargy	3	0
Dizziness	3	2
Dystonia	2	1
Respiratory, Thoracic, and Mediastinal Disorders		
Epistaxis	2	1
Skin and Subcutaneous Tissue Disorders		
Rash	2	1

[a] Adverse reactions reported by at least 2% of pediatric patients treated with oral ABILIFY, except adverse reactions which had an incidence equal to or less than placebo.

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 ABILIFY 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 ABILIFY-treated patients and 2% for adjunctive placebo-treated patients.

Commonly Observed Adverse Reactions

The commonly observed adverse reactions associated with the use of adjunctive ABILIFY in patients with major depressive disorder (incidence of 5% or greater and ABILIFY 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 23 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 ABILIFY (doses ≥2 mg/day) and for which the incidence in patients treated with adjunctive ABILIFY was greater than the incidence in patients treated with adjunctive placebo in the combined dataset.

Table 23: Adverse Reactions in Short-Term, Placebo-Controlled Adjunctive Trials in Patients with Major Depressive Disorder

	Percentage of Patients Reporting Reaction[a]	
System Organ Class **Preferred Term**	**ABILIFY + ADT*** **(n=371)**	**Placebo + ADT*** **(n=366)**
Eye Disorders		
Blurred Vision	6	1
Gastrointestinal Disorders		
Constipation	5	2
General Disorders and Administration Site Conditions		
Fatigue	8	4
Feeling Jittery	3	1
Infections and Infestations		
Upper Respiratory Tract Infection	6	4
Investigations		
Weight Increased	3	2
Metabolism and Nutrition Disorders		
Increased Appetite	3	2
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	4	3
Myalgia	3	1
Nervous System Disorders		
Akathisia	25	4
Somnolence	6	4
Tremor	5	4

Sedation	4	2
Dizziness	4	2
Disturbance in Attention	3	1
Extrapyramidal Disorder	2	0
Psychiatric Disorders		
Restlessness	12	2
Insomnia	8	2

[a] Adverse reactions reported by at least 2% of patients treated with adjunctive ABILIFY, 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 ABILIFY injection was administered at doses of 5.25 mg to 15 mg.

Commonly Observed Adverse Reactions

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

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

Table 24 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 ABILIFY injection (doses ≥5.25 mg/day) and for which the incidence in patients treated with ABILIFY injection was greater than the incidence in patients treated with placebo in the combined dataset.

Table 24: Adverse Reactions in Short-Term, Placebo-Controlled Trials in Patients Treated with ABILIFY Injection

	Percentage of Patients Reporting Reaction[a]	
System Organ Class **Preferred Term**	**ABILIFY** **(n=501)**	**Placebo** **(n=220)**
Cardiac Disorders		
Tachycardia	2	<1
Gastrointestinal Disorders		
Nausea	9	3
Vomiting	3	1
General Disorders and Administration Site Conditions		
Fatigue	2	1
Nervous System Disorders		

Headache	12	7
Dizziness	8	5
Somnolence	7	4
Sedation	3	2
Akathisia	2	0

[a] Adverse reactions reported by at least 2% of patients treated with ABILIFY 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, 5, 10, 15, 20, and 30 mg/day) of oral ABILIFY 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%).

Tourette's Disorder

In a study of pediatric patients (7 to 17 years of age) with Tourette's disorder, no common adverse reaction(s) had a dose response relationship.

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 ABILIFY-treated patients was 13% vs. 12% for placebo; and the incidence of akathisia-related events for ABILIFY-treated patients was 8% vs. 4% for placebo. In the short-term, placebo-controlled trial of schizophrenia in pediatric patients (13 to 17 years), the incidence of reported EPS-related events, excluding events related to akathisia, for ABILIFY-treated patients was 25% vs. 7% for placebo; and the incidence of akathisia-related events for ABILIFY-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 ABILIFY and placebo, with the exception of the Barnes Akathisia Scale (ABILIFY, 0.08; placebo, –0.05). In the pediatric (13 to 17 years) schizophrenia trial, the objectively collected data did not show a difference between ABILIFY and placebo, with the exception of the Simpson Angus Rating Scale (ABILIFY, 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 ABILIFY 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 ABILIFY-treated patients was 16% vs. 8% for placebo and the incidence of akathisia-related events for monotherapy ABILIFY-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 ABILIFY-treated patients was 15% vs. 8% for adjunctive placebo and the incidence of akathisia-related events for adjunctive ABILIFY-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 ABILIFY-treated patients was 26% vs. 5% for placebo and the incidence of akathisia-related events for ABILIFY-treated patients was 10% vs. 2% for placebo.

In the adult bipolar mania trials with monotherapy ABILIFY, the Simpson Angus Rating Scale and the Barnes Akathisia Scale showed a significant difference between ABILIFY and placebo (ABILIFY, 0.50; placebo, –0.01 and ABILIFY, 0.21; placebo, –0.05). Changes in the Assessments of Involuntary Movement Scales were similar for the ABILIFY and placebo groups. In the bipolar mania trials with ABILIFY as adjunctive therapy with either lithium or valproate, the Simpson Angus Rating Scale and the Barnes Akathisia Scale showed a significant difference between adjunctive ABILIFY and adjunctive placebo (ABILIFY, 0.73; placebo, 0.07 and ABILIFY, 0.30; placebo, 0.11). Changes in the Assessments of Involuntary Movement Scales were similar for adjunctive ABILIFY 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 ABILIFY and placebo (ABILIFY, 0.90; placebo, −0.05). Changes in the Barnes Akathisia Scale and the Assessments of Involuntary Movement Scales were similar for the ABILIFY 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 ABILIFY-treated patients was 8% vs. 5% for adjunctive placebo-treated patients; and the incidence of akathisia-related events for adjunctive ABILIFY-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 ABILIFY and adjunctive placebo (ABILIFY, 0.31; placebo, 0.03 and ABILIFY, 0.22; placebo, 0.02). Changes in the Assessments of Involuntary Movement Scales were similar for the adjunctive ABILIFY 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 ABILIFY-treated patients was 18% vs. 2% for placebo and the incidence of akathisia-related events for ABILIFY-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 ABILIFY and placebo (ABILIFY, 0.1; placebo, –0.4). Changes in the Barnes Akathisia Scale and the Assessments of Involuntary Movement Scales were similar for the ABILIFY and placebo groups.

Tourette's Disorder

In the short-term, placebo-controlled trials in Tourette's disorder in pediatric patients (6 to 18 years), the incidence of reported EPS-related events, excluding events related to akathisia, for ABILIFY-treated patients was 7% vs. 6% for placebo and the incidence of akathisia-related events for ABILIFY-treated patients was 4% vs. 6% for placebo.

In the pediatric (6 to 18 years) short-term Tourette's disorder trials, changes in the Simpson Angus Rating Scale, Barnes Akathisia Scale and Assessments of Involuntary Movement Scale were not clinically meaningfully different for ABILIFY and placebo.

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 ABILIFY-treated patients was 2% vs. 2% for placebo and the incidence of akathisia-related events for ABILIFY-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 ABILIFY and placebo.

Dystonia

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.

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 ≤49 days), and were of limited duration (7/12 ≤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 monotherapy study and a long-term adjunctive study with lithium and valproate in bipolar disorder.

Other Adverse Reactions Observed During the Premarketing Evaluation of ABILIFY

The following listing does not include reactions: 1) already listed in previous tables or elsewhere in labeling, 2) for which a drug cause was remote, 3) which were so general as to be uninformative, 4) which were not considered to have significant clinical implications, or 5) which occurred at a rate equal to or less than placebo.

Reactions are categorized by body system according to the following definitions: *frequent* adverse reactions are those occurring in at least 1/100 patients; *infrequent* adverse reactions are those occurring in 1/100 to 1/1000 patients; *rare* reactions are those occurring in fewer than 1/1000 patients:

Adults - Oral Administration

Blood and Lymphatic System Disorders:

rare - thrombocytopenia

Cardiac Disorders:

infrequent – bradycardia, palpitations, *rare* – atrial flutter, cardio-respiratory arrest, atrioventricular block, atrial fibrillation, angina pectoris, myocardial ischemia, myocardial infarction, cardiopulmonary failure

Eye Disorders:

infrequent – photophobia; *rare* - diplopia

Gastrointestinal Disorders:

infrequent - gastroesophageal reflux disease

General Disorders and Administration Site Conditions:

frequent - asthenia; *infrequent* – peripheral edema, chest pain; *rare* – face edema

Hepatobiliary Disorders:

rare - hepatitis, jaundice

Immune System Disorders:

rare- hypersensitivity

Injury, Poisoning, and Procedural Complications:

infrequent– fall; *rare* – heat stroke

Investigations:

frequent - weight decreased, *infrequent* - hepatic enzyme increased, blood glucose increased, blood lactate dehydrogenase increased, gamma glutamyl transferase increased; *rare* – blood prolactin increased, blood urea inceased, blood creatinine increased, blood bilirubin increased, electrocardiogram QT prolonged, glycosylated hemoglobin increased

Metabolism and Nutrition Disorders:

frequent –anorexia; *infrequent* - *rare* - hypokalemia, hyponatremia, hypoglycemia

Musculoskeletal and Connective Tissue Disorders:

infrequent - muscular weakness, muscle tightness; *rare* – rhabdomyolysis, mobility decreased

Nervous System Disorders:

infrequent - parkinsonism, memory impairment, cogwheel rigidity, hypokinesia, myoclonus, bradykinesia; *rare* – akinesia, myoclonus, coordination abnormal, speech disorder, Grand Mal convulsion; *<1/10,000 patients* - choreoathetosis

Psychiatric Disorders:

infrequent – aggression, loss of libido, delirium; *rare* – libido increased, anorgasmia, tic, homicidal ideation, catatonia, sleep walking

Renal and Urinary Disorders:

rare - urinary retention, nocturia

Reproductive System and Breast Disorders:

infrequent - erectile dysfunction; *rare* – gynaecomastia, menstruation irregular, amenorrhea, breast pain, priapism

Respiratory, Thoracic, and Mediastinal Disorders:

infrequent - nasal congestion, dyspnea

Skin and Subcutaneous Tissue Disorders:

infrequent - rash, hyperhidrosis, pruritus, photosensitivity reaction, alopecia; *rare* - urticaria

Vascular Disorders:

infrequent – hypotension, hypertension

Pediatric Patients - Oral Administration

Most adverse events observed in the pooled database of 1,686 pediatric patients, aged 6 to 18 years, were also observed in the adult population. Additional adverse reactions observed in the pediatric population are listed below.

Eye Disorders

infrequent - oculogyric crisis

Gastrointestinal Disorders:

infrequent -tongue dry, tongue spasm

Investigations:

frequent - blood insulin increased

Nervous System Disorders:

infrequent - sleep talking

Renal and Urinary Disorders

frequent – enuresis

Skin and Subcutaneous Tissue Disorders:

infrequent - hirsutism

Adults - Intramuscular Injection

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

General Disorders and Administration Site Conditions:

≥1/100 patients - injection site reaction; *≥1/1000 patients and <1/100 patients* - venipuncture site bruise

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval 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: occurrences of allergic reaction (anaphylactic reaction, angioedema, laryngospasm, pruritus/urticaria, or oropharyngeal spasm), and blood glucose fluctuation.

7 DRUG INTERACTIONS

7.1 Drugs Having Clinically Important Interactions with ABILIFY

Table 25: Clinically Important Drug Interactions with ABILIFY:

Concomitant Drug Name or Drug Class	Clinical Rationale	Clinical Recommendation
Strong CYP3A4 Inhibitors (e.g., itraconazole, clarithromycin) or strong CYP2D6 inhibitors (e.g., quinidine, fluoxetine, paroxetine)	The concomitant use of ABILIFY with strong CYP 3A4 or CYP2D6 inhibitors increased the exposure of aripiprazole compared to the use of ABILIFY alone *[see CLINICAL PHARMACOLOGY (12.3)]*.	With concomitant use of ABILIFY with a strong CYP3A4 inhibitor or CYP2D6 inhibitor, reduce the ABILIFY dosage *[see DOSAGE AND ADMINISTRATION (2.7)]*.
Strong CYP3A4 Inducers (e.g., carbamazepine, rifampin)	The concomitant use of ABILIFY and carbamazepine decreased the exposure of aripiprazole compared to the use of ABILIFY alone *[see CLINICAL PHARMACOLOGY (12.3)]*.	With concomitant use of ABILIFY with a strong CYP3A4 inducer, consider increasing the ABILIFY dosage *[see DOSAGE AND ADMINISTRATION (2.7)]*.
Antihypertensive Drugs	Due to its alpha adrenergic antagonism, aripiprazole has the potential to enhance the effect of certain antihypertensive agents.	Monitor blood pressure and adjust dose accordingly *[see WARNINGS AND PRECAUTIONS (5.7)]*.
Benzodiazepines (e.g., lorazepam)	The intensity of sedation was greater with the combination of oral aripiprazole and lorazepam as compared to that observed with aripiprazole alone. The orthostatic hypotension observed was greater with the combination as compared to that observed with lorazepam alone *[see WARNINGS AND PRECAUTIONS (5.7)]*	Monitor sedation and blood pressure. Adjust dose accordingly.

7.2 Drugs Having No Clinically Important Interactions with ABILIFY

Based on pharmacokinetic studies, no dosage adjustment of ABILIFY is required when administered concomitantly with famotidine, valproate, lithium, lorazepam.

In addition, no dosage adjustment is necessary for substrates of CYP2D6 (e.g., dextromethorphan, fluoxetine, paroxetine, or venlafaxine), CYP2C9 (e.g., warfarin), CYP2C19 (e.g., omeprazole, warfarin, escitalopram), or CYP3A4 (e.g., dextromethorphan) when co-administered with ABILIFY. Additionally, no dosage adjustment is necessary for valproate, lithium, lamotrigine, lorazepam, or sertraline when co-administered with ABILIFY. *[see CLINICAL PHARMACOLOGY (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ABILIFY during pregnancy. For more information contact the National Pregnancy Registry for Atypical Antipsychotics at 1-866-961-2388 or visit http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/.

Risk Summary

Neonates exposed to antipsychotic drugs (including ABILIFY) during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms. Adequate and well controlled studies with ABILIFY have not been conducted in pregnant women. Animal reproduction studies were conducted with aripiprazole in rats and rabbits during organogenesis, and in rats during the pre-and post-natal period. Oral and intravenous aripiprazole administration during organogenesis in rats and/or rabbits at doses higher than the maximum recommended human dose (MRHD) produced fetal death, decreased fetal weight, undescended testicles, delayed skeletal ossification, skeletal abnormalities, and diaphragmatic hernia. Oral and intravenous aripiprazole administration during the pre- and post-natal period in rats at doses higher than the maximum recommended human dose (MRHD) produced prolonged gestation, stillbirths, decreased pup weight, and decreased pup survival. Administer ABILIFY during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Extrapyramidal and/or withdrawal symptoms, including agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder have been reported in neonates who were exposed to antipsychotic drugs (including ABILIFY) during the third trimester of pregnancy. These symptoms have varied in severity. Some neonates recovered within hours or days without specific treatment; others required prolonged hospitalization. Monitor neonates for extrapyramidal and/or withdrawal symptoms.

Data

Animal Data

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

Pregnant rats were treated with oral doses of 3, 10, and 30 mg/kg/day (1, 3, and 10 times the maximum recommended human dose [MRHD] on a mg/m^2 basis) of aripiprazole during the period of organogenesis. Gestation was slightly prolonged at 30 mg/kg/day. Treatment at the high dose of 30 mg/kg/day caused a slight delay in fetal development (decreased fetal weight), undescended testes, and delayed skeletal ossification (also seen at 10 mg/kg/day). There were no adverse effects on embryofetal or pup survival. Delivered offspring had decreased body weights (10 and 30 mg/kg/day), and increased incidences of hepatodiaphragmatic nodules and diaphragmatic hernia at 30 mg/kg (the other dose groups were not examined for these findings). Postnatally, delayed vaginal opening was seen at 10 and 30 mg/kg/day 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/day. Some maternal toxicity was seen at 30 mg/kg/day however, there was no evidence to suggest that these developmental effects were secondary to maternal toxicity.

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

Pregnant rabbits were treated with oral doses of 10, 30 , and 100 mg/kg/day (2 , 3, and 11 times human exposure at MRHD based on AUC and 6, 19 , and 65 times the MRHD based on mg/m^2) of aripiprazole during the period of organogenesis. At the high dose of 100 mg/kg/day decreased maternal food consumption, and increased abortions were seen as well as increased fetal mortality, decreased fetal weight (also seen at 30 mg/kg/day), increased incidence of a skeletal abnormality (fused sternebrae) (also seen at 30 mg/kg/day).

In pregnant rabbits receiving aripiprazole injection intravenously (3, 10, 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/day, which is 5 times the human exposure at the MRHD based on AUC and is 6 times the MRHD based on mg/m2.

In a study in which rats were treated peri- and post-natally with oral doses of 3, 10, and 30 mg/kg/day (1, 3, and 10 times the MRHD on a mg/m2 basis) of aripiprazole from gestation day 17 through day 21 postpartum, slight maternal toxicity, slightly prolonged gestation an increase in stillbirths and, decreases in pup weight (persisting into adulthood) and survival were seen at 30 mg/kg/day.

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

8.3 Nursing Mothers

ABILIFY is present in human breast milk. Because of the potential for serious adverse reactions in nursing infants from ABILIFY, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

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.

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 weight *[see CLINICAL PHARMACOLOGY (12.3)]*.

Schizophrenia

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 DOSAGE AND ADMINISTRATION (2.1), ADVERSE REACTIONS (6.1)*, 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.

Bipolar I Disorder

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 DOSAGE AND ADMINISTRATION (2.2), ADVERSE REACTIONS (6.1), 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.

Irritability Associated with Autistic Disorder

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), DOSAGE AND ADMINISTRATION (2.4), ADVERSE REACTIONS (6.1), and CLINICAL STUDIES (14.4)]*. A maintenance trial was conducted in pediatric patients (6 to 17 years of age) with irritability associated with autistic disorder. The first phase of this trial was an open-label, flexibly dosed (aripiprazole 2 to 15 mg/day) phase in which patients were stabilized (defined as > 25% improvement on the ABC-I subscale, and a CGI-I rating of "much improved" or "very much improved") on ABILIFY for 12 consecutive weeks. Overall, 85 patients were stabilized and entered the second, 16-week, double-blind phase where they were randomized to either continue ABILIFY treatment or switch to placebo. In this trial, the efficacy of ABILIFY for the maintenance treatment of irritability associated with autistic disorder was not established.

Tourette's Disorder

Safety and effectiveness of aripiprazole in pediatric patients with Tourette's Disorder were established in one 8-week (aged 7 to 17) and one 10-week trial (aged 6 to 18) in 194 pediatric patients *[see DOSAGE AND ADMINISTRATION (2.5), ADVERSE REACTIONS (6.1), and CLINICAL STUDIES (14.5)]*. Maintenance efficacy in pediatric patients has not been systematically evaluated.

Juvenile Animal Studies

Aripiprazole in juvenile rats caused mortality, CNS clinical signs, impaired memory and learning, and delayed sexual maturation when administered at oral doses of 10, 20,

40 mg/kg/day from weaning (21 days old) through maturity (80 days old). At 40 mg/kg/day, mortality, decreased activity, splayed hind limbs, hunched posture, ataxia, tremors and other CNS signs were observed in both genders. In addition, delayed sexual maturation was observed in males. At all doses and in a dose-dependent manner, impaired memory and learning, increased motor activity, and histopathology changes in the pituitary (atrophy), adrenals (adrenocortical hypertrophy), mammary glands (hyperplasia and increased secretion), and female reproductive organs (vaginal mucification, endometrial atrophy, decrease in ovarian corpora lutea) were observed. The changes in female reproductive organs were considered secondary to the increase in prolactin serum levels. A No Observed Adverse Effect Level (NOAEL) could not be determined and, at the lowest tested dose of 10 mg/kg/day, there is no safety margin relative to the systemic exposures (AUC0-24) for aripiprazole or its major active metabolite in adolescents at the maximum recommended pediatric dose of 15 mg/day. All drug-related effects were reversible after a 2-month recovery period, and most of the drug effects in juvenile rats were also observed in adult rats from previously conducted studies.

Aripiprazole in juvenile dogs (2 months old) caused CNS clinical signs of tremors, hypoactivity, ataxia, recumbency and limited use of hind limbs when administered orally for 6 months at 3, 10, 30 mg/kg/day. Mean body weight and weight gain were decreased up to 18% in females in all drug groups relative to control values. A NOAEL could not be determined and, at the lowest tested dose of 3 mg/kg/day, there is no safety margin relative to the systemic exposures (AUC0-24) for aripiprazole or its major active metabolite in adolescents at the maximum recommended pediatric dose of 15 mg/day. All drug-related effects were reversible after a 2-month recovery period.

8.5 Geriatric Use

No dosage adjustment is recommended for elderly patients *[see also BOXED WARNING, WARNINGS AND PRECAUTIONS (5.1), and CLINICAL PHARMACOLOGY (12.3)]*.

Of the 13,543 patients treated with oral ABILIFY in clinical trials, 1073 (8%) were ≥65 years old and 799 (6%) were ≥75 years old. Placebo-controlled studies of oral ABILIFY 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 ABILIFY injection in clinical trials, 99 (13%) were ≥65 years old and 78 (10%) were ≥75 years old. Placebo-controlled studies of ABILIFY 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.

ABILIFY is not approved for the treatment of patients with psychosis associated with Alzheimer's disease *[see also BOXED WARNING and WARNINGS AND PRECAUTIONS (5.1)]*.

8.6 CYP2D6 Poor Metabolizers

Dosage adjustment is recommended in known CYP2D6 poor metabolizers due to high aripiprazole concentrations. Approximately 8% of Caucasians and 3–8% of Black/African Americans cannot metabolize CYP2D6 substrates and are classified as poor metabolizers (PM) *[see DOSAGE AND ADMINISTRATION (2.7) and CLINICAL PHARMACOLOGY (12.3)]*.

8.7 Hepatic and Renal Impairment

No dosage adjustment for ABILIFY is required on the basis of a patient's hepatic function (mild to severe hepatic impairment, Child-Pugh score between 5 and 15), or renal function (mild to severe renal impairment, glomerular filtration rate between 15 and 90 mL/minute) *[see CLINICAL PHARMACOLOGY (12.3)]*.

8.8 Other Specific Populations

No dosage adjustment for ABILIFY is required on the basis of a patient's sex, race, or smoking status *[see CLINICAL PHARMACOLOGY (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

ABILIFY is not a controlled substance.

9.2 Abuse and Dependence

ABILIFY 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 (e.g., 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

In clinical trials and in postmarketing experience, adverse reactions of deliberate or accidental overdosage with oral ABILIFY have been reported worldwide. These include overdoses with oral ABILIFY alone and in combination with other substances. No fatality was reported with ABILIFY alone. The largest known dose with a known outcome involved acute ingestion of 1260 mg of oral ABILIFY (42 times the maximum recommended daily dose) by a patient who fully recovered. Deliberate or accidental overdosage was also reported in children (age 12 and younger) involving oral ABILIFY ingestions up to 195 mg with no fatalities.

Common adverse reactions (reported in at least 5% of all overdose cases) reported with oral ABILIFY overdosage (alone or in combination with other substances) include vomiting, somnolence, and tremor. Other clinically important signs and symptoms observed in one or more patients with ABILIFY 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

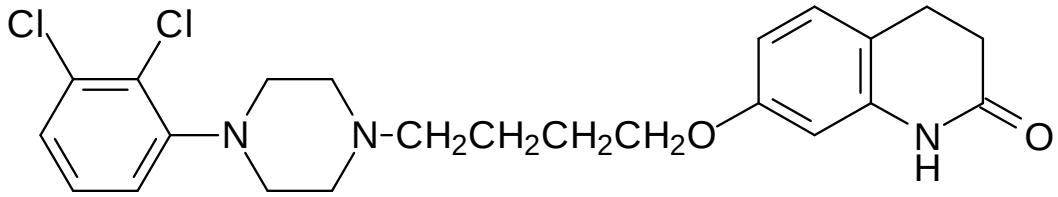
No specific information is available on the treatment of overdose with ABILIFY. An electrocardiogram should be obtained in case of overdosage and if QT interval prolongation is present, cardiac monitoring should be instituted. Otherwise, management of overdose should concentrate on supportive therapy, 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 ABILIFY, decreased the mean AUC and Cmax of aripiprazole by 50%.

Hemodialysis: Although there is no information on the effect of hemodialysis in treating an overdose with ABILIFY, 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® (aripiprazole) Tablets, ABILIFY DISCMELT® (aripiprazole) Orally Disintegrating Tablets, ABILIFY® (aripiprazole) Oral Solution, and ABILIFY® (aripiprazole) Injection, a solution for intramuscular injection. Aripiprazole is 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydrocarbostyril. The empirical formula is C23H27Cl2N3O2 and its molecular weight is 448.38. 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 199.5mg of sulfobutylether β-cyclodextrin (SBECD), 10.4 mg of tartaric acid, qs to pH 4.3 of sodium hydroxide, and qs to 1.33 mL of water for injection.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of aripiprazole in schizophrenia or bipolar mania, is unknown. However, the efficacy of aripiprazole could be mediated through a combination of partial agonist activity at D2 and 5-HT_{1A} receptors and antagonist activity at 5-HT_{2A} receptors. Actions at receptors other than D2, 5-HT_{1A}, and 5-HT_{2A} may explain some of the other clinical effects of aripiprazole (e.g., the orthostatic hypotension observed with aripiprazole may be explained by its antagonist activity at adrenergic alpha1 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, alpha1-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 is dose-proportional. Elimination of aripiprazole is mainly through hepatic metabolism involving two P450 isozymes, CYP2D6 and CYP3A4. For CYP2D6 poor metabolizers, the mean elimination half-life for aripiprazole is about 146 hours.

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 Cmax or AUC of aripiprazole or its active metabolite, dehydro-aripiprazole, but delayed Tmax 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 Cmax 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 to 30 mg/day aripiprazole for 14 days, there was dose-dependent D2 receptor occupancy indicating brain penetration of aripiprazole in humans.

Metabolism and Elimination

Aripiprazole is metabolized primarily by three biotransformation pathways: dehydrogenation, hydroxylation, and N-dealkylation. Based on in vitro studies, CYP3A4 and CYP2D6 enzymes are responsible for dehydrogenation and hydroxylation of aripiprazole, and N-dealkylation is catalyzed by CYP3A4. Aripiprazole is the predominant drug moiety in the systemic circulation. At steady-state, dehydro-aripiprazole, the active metabolite, represents about 40% of aripiprazole AUC in plasma.

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

Drug Interaction Studies

Effects of other drugs on the exposures of aripiprazole and dehydro-aripiprazole are summarized in Figure 1 and Figure 2, respectively. Based on simulation, a 4.5-fold increase in mean Cmax and AUC values at steady-state is expected when extensive metabolizers of CYP2D6 are administered with both strong CYP2D6 and CYP3A4 inhibitors. A 3-fold increase in mean Cmax and AUC values at steady-state is expected in poor metabolizers of CYP2D6 administered with strong CYP3A4 inhibitors.

Figure 1: The effects of other drugs on aripiprazole pharmacokinetics

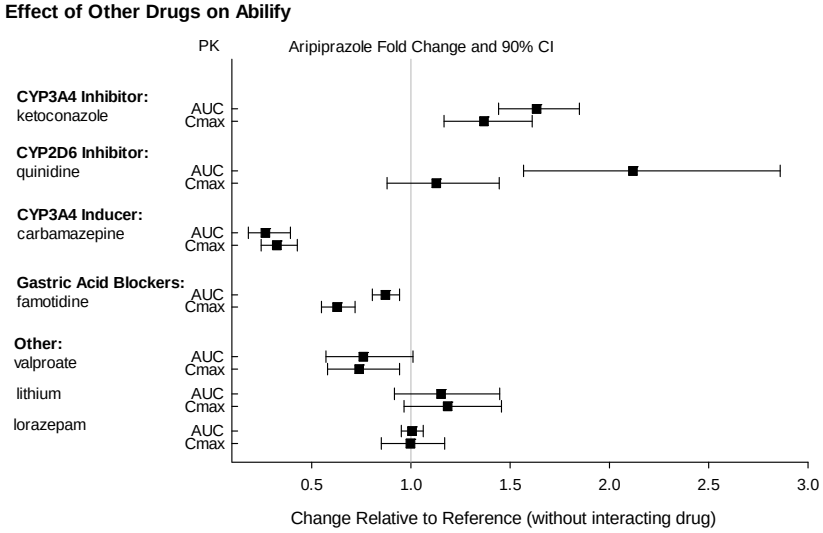
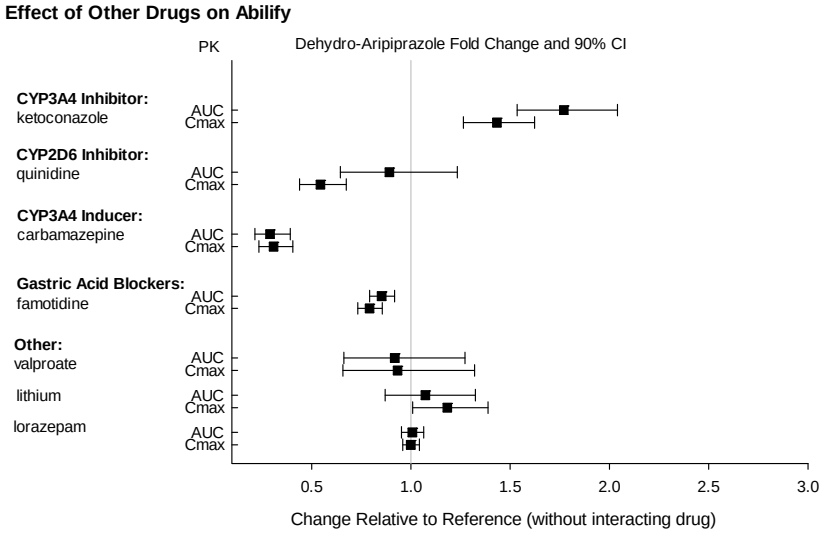


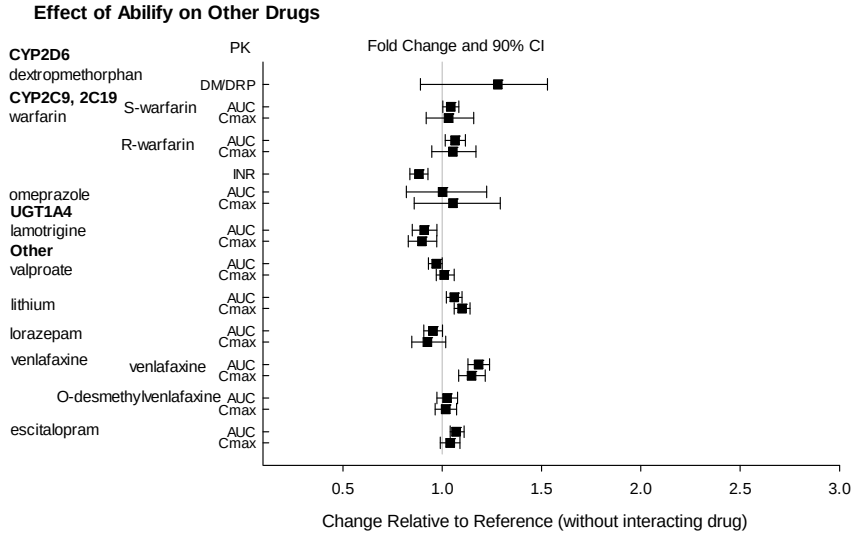
Figure 2: The effects of other drugs on dehydro-aripiprazole pharmacokinetics



The effects of ABILIFY on the exposures of other drugs are summarized in Figure 3. A population PK analysis in patients with major depressive disorder showed no substantial change in plasma concentrations of fluoxetine (20 or 40 mg/day), paroxetine CR (37.5 or 50 mg/day), or sertraline (100 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.

Figure 3: The effects of ABILIFY on pharmacokinetics of other drugs



Studies in Specific Populations

Exposures of aripiprazole and dehydro-aripiprazole in specific populations are summarized in Figure 4 and Figure 5, respectively. In addition, in pediatric patients (10 to 17 years of age) administered with Abilify (20 mg to 30 mg), the body weight corrected aripiprazole clearance was similar to the adults.

Figure 4: Effects of intrinsic factors on aripiprazole pharmacokinetics

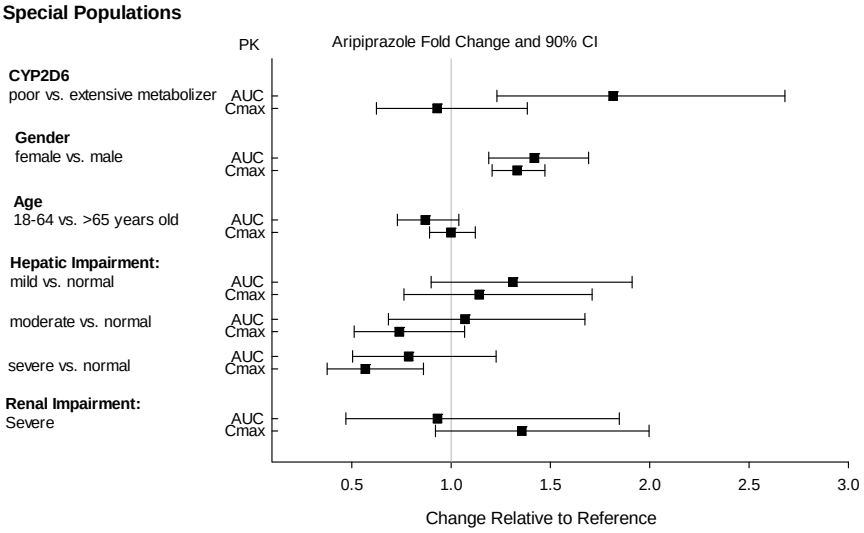
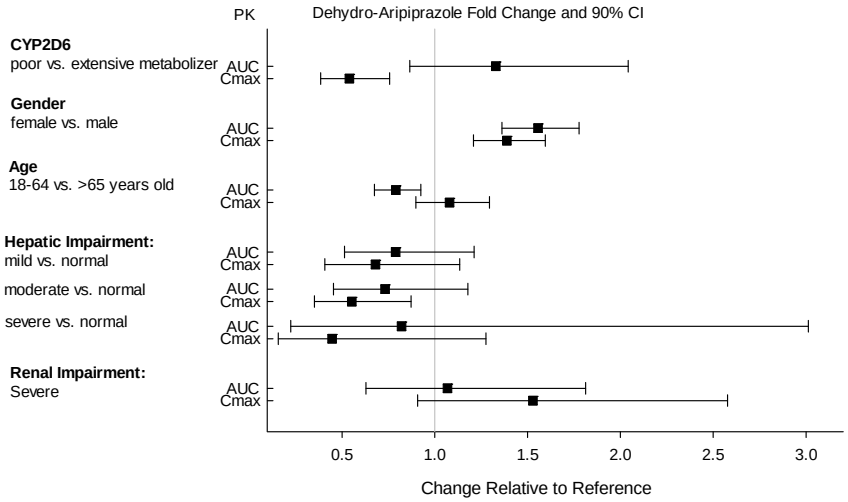


Figure 5: Effects of intrinsic factors on dehydro-aripiprazole pharmacokinetics



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 Cmax 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, Sprague-Dawley (SD) rats, and F344 rats. Aripiprazole was administered for 2 years in the diet at doses of 1, 3, 10, and 30 mg/kg/day to ICR mice and 1, 3, and 10 mg/kg/day to F344 rats (0.2 to 5 times and 0.3 to 3 times the maximum recommended human dose [MRHD] based on mg/m^2, respectively). In addition, SD rats were dosed orally for 2 years at 10, 20, 40, and 60 mg/kg/day (3 to 19 times the MRHD based on mg/m2). Aripiprazole did not induce tumors in male mice or male rats. In female mice, the incidences of pituitary gland

adenomas and mammary gland adenocarcinomas and adenoacanthomas were increased at dietary doses of 3 to 30 mg/kg/day (0.1 to 0.9 times human exposure at MRHD based on AUC and 0.5 to 5 times the MRHD based on mg/m^2). In female rats, the incidence of mammary gland fibroadenomas was increased at a dietary dose of 10 mg/kg/day (0.1 times human exposure at MRHD based on AUC and 3 times the MRHD based on mg/m^2); and the incidences of adrenocortical carcinomas and combined adrenocortical adenomas/carcinomas were increased at an oral dose of 60 mg/kg/day (14 times human exposure at MRHD based on AUC and 19 times the MRHD based on mg/m^2).

Proliferative changes in the pituitary and mammary gland of rodents have been observed following chronic administration of other antipsychotic agents and are considered prolactin-mediated. Serum prolactin was not measured in the aripiprazole carcinogenicity studies. However, increases in serum prolactin levels were observed in female mice in a 13-week dietary study at the doses associated with mammary gland and pituitary tumors. Serum prolactin was not increased in female rats in 4-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, 6, and 20 mg/kg/day (0.6, 2, and 6 times the maximum recommended human dose [MRHD] on a mg/m2 basis) of aripiprazole from 2 weeks prior to mating through day 7 of gestation. Estrus cycle irregularities and increased corpora lutea were seen at all doses, but no impairment of fertility was seen. Increased pre-implantation loss was seen at 6 and 20 mg/kg/day and decreased fetal weight was seen at 20 mg/kg/day.

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

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 and 60 mg/kg. The 40 and 60 mg/kg/day doses are 13 and 19 times the maximum recommended human dose (MRHD) based on mg/m^2 and 7 to 14 times human exposure at MRHD based on AUC. Evaluation of the retinas of albino mice and of monkeys did not reveal evidence of retinal degeneration. Additional studies to further evaluate the mechanism have not been performed. The relevance of this finding to human risk is unknown.

14 CLINICAL STUDIES

Efficacy of the oral formulations of ABILIFY (aripiprazole) was established in the following adequate and well-controlled trials:

- Four short-term trials and one maintenance trial in adult patients and one short-term trial in adolescents (ages 13-17) with schizophrenia (14.1)
- Four short-term monotherapy trials and one 6-week adjunctive trial in adult patients and one short-term monotherapy trial in pediatric patients (ages 10-17) with manic or mixed episodes (14.2)
- One maintenance monotherapy trial and in one maintenance adjunctive trial in adult patients with bipolar I disorder (14.2)
- Two short-term trials in adult patients with MDD who had an inadequate response to antidepressant therapy during the current episode (14.3)
- Two short-term trials in pediatric patients (ages 6-17 years) for the treatment of irritability associated with autistic disorder (14.4)
- Two short-term trials in pediatric patients (ages 6-18 years) with Tourette's disorder (14.5)

Efficacy of the injectable formulation of ABILIFY (aripiprazole) was established in the following adequate and well-controlled trials:

- Three 24-hour trials in agitated adult patients with schizophrenia or manic/mixed episodes of bipolar I disorder (14.6)

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 ABILIFY 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. Efficacy was evaluated using the total score on the Positive and Negative Syndrome Scale (PANSS). The PANSS is a 30 item scale that measures positive symptoms of schizophrenia (7 items), negative symptoms of schizophrenia (7 items), and general psychopathology (16 items), each rated on a scale of 1 (absent) to 7 (extreme); total PANSS scores range from 30 to 210. The Clinical Global Impression (CGI) assessment reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient.

In a 4-week trial (n=414) comparing two fixed doses of ABILIFY (15 or 30 mg/day) to placebo, both doses of ABILIFY were superior to placebo in the PANSS total score (Study 1 in Table 26), PANSS positive subscale, and CGI-severity score. In addition, the 15 mg dose was superior to placebo in the PANSS negative subscale.

In a 4-week trial (n=404) comparing two fixed doses of ABILIFY (20 or 30 mg/day) to placebo, both doses of ABILIFY were superior to placebo in the PANSS total score (Study 2 in Table 26), PANSS positive subscale, PANSS negative subscale, and CGI-severity score.

In a 6-week trial (n=420) comparing three fixed doses of ABILIFY (10, 15, or 20 mg/day) to placebo, all three doses of ABILIFY were superior to placebo in the PANSS total score (Study 3 in Table 26), PANSS positive subscale, and the PANSS negative subscale.

In a 6-week trial (n=367) comparing three fixed doses of ABILIFY (2, 5, or 10 mg/day) to placebo, the 10 mg dose of ABILIFY was superior to placebo in the PANSS total score (Study 4 in Table 26), the primary outcome measure of the study. The 2 and 5 mg doses did not demonstrate superiority to placebo on the primary outcome measure.

Thus, the efficacy of 10, 15, 20, 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 ≥5 (minimally worse), scores ≥5 (moderately severe) on the hostility or uncooperativeness items of the PANSS, or ≥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 (Study 5 in Figure 6).

Pediatric Patients

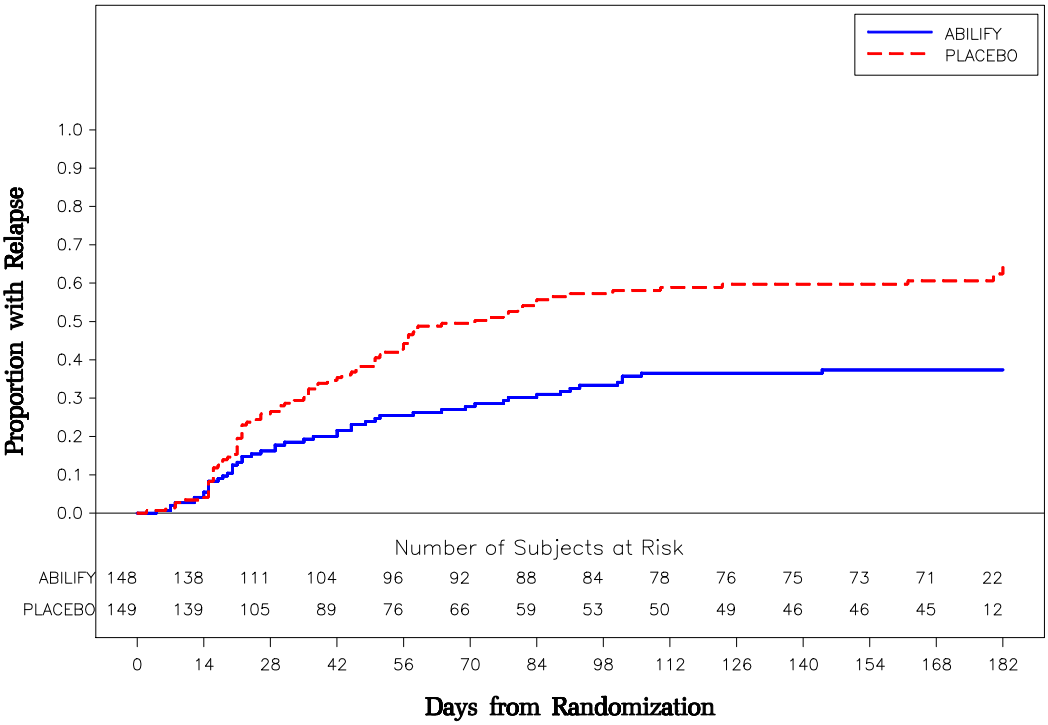
The efficacy of ABILIFY (aripiprazole) in the treatment of schizophrenia in pediatric patients (13 to 17 years of age) was evaluated in one 6-week, placebo-controlled trial of outpatients who met DSM-IV criteria for schizophrenia and had a PANSS score ≥70 at baseline. In this trial (n=302) comparing two fixed doses of ABILIFY (10 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 (Study 6 in Table 26), 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.

Table 26: Schizophrenia Studies

Study Number	Treatment Group	Primary Efficacy Measure: PANSS		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
Study 1	ABILIFY (15 mg/day)*	98.5 (17.2)	-15.5 (2.40)	-12.6 (-18.9, -6.2)
	ABILIFY (30 mg/day)*	99.0 (19.2)	-11.4 (2.39)	-8.5 (-14.8, -2.1)
	Placebo	100.2 (16.5)	-2.9 (2.36)	--
Study 2	ABILIFY (20 mg/day)*	92.6 (19.5)	-14.5 (2.23)	-9.6 (-15.4, -3.8)
	ABILIFY (30 mg/day)*	94.2 (18.5)	-13.9 (2.24)	-9.0 (-14.8, -3.1)
	Placebo	94.3 (18.5)	-5.0 (2.17)	--
Study 3	ABILIFY (10 mg/day)*	92.7 (19.5)	-15.0 (2.38)	-12.7 (-19.00, -6.41)
	ABILIFY (15 mg/day)*	93.2 (21.6)	-11.7 (2.38)	-9.4 (-15.71, -3.08)
	ABILIFY (20 mg/day)*	92.5 (20.9)	-14.4 (2.45)	-12.1 (-18.53, -5.68)
	Placebo	92.3 (21.8)	-2.3 (2.35)	--
Study 4	ABILIFY (2 mg/day)	90.7 (14.5)	-8.2 (1.90)	-2.9 (-8.29, 2.47)
	ABILIFY (5 mg/day)	92.0 (12.6)	-10.6 (1.93)	-5.2 (-10.7, 0.19)
	ABILIFY (10 mg/day)*	90.0 (11.9)	-11.3 (1.88)	-5.9 (-11.3, -0.58)
	Placebo	90.8 (13.3)	-5.3 (1.97)	--
Study 6 (Pediatric, 13-17 years)	ABILIFY (10 mg/day)*	93.6 (15.7)	-26.7 (1.91)	-5.5 (-10.7, -0.21)
	ABILIFY (30 mg/day)*	94.0 (16.1)	-28.6 (1.92)	-7.4 (-12.7, -2.13)
	Placebo	94.6 (15.6)	-21.2 (1.93)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval.
[a] Difference (drug minus placebo) in least-squares mean change from baseline.
* Doses statistically significantly superior to placebo.

Figure 6: Kaplan-Meier Estimation of Cumulative Proportion of Patients with Relapse (Schizophrenia Study 5)



14.2 Bipolar Disorder

Acute Treatment of Manic and Mixed Episodes

Adults

Monotherapy

The efficacy of ABILIFY as monotherapy 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 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 30 mg/day in two studies and 15 mg/day in two studies), ABILIFY was superior to placebo in the reduction of Y-MRS total score (Studies 1-4 in Table 27) 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.

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 to 1.0 mEq/L) or valproate (50 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 ≥16 and ≤25% improvement on the Y-MRS total score) to lithium or valproate were randomized to receive either ABILIFY (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 to 1.0 mEq/L or 50 to 125 μg/mL, respectively) was superior to lithium or valproate with adjunctive placebo in the reduction of the Y-MRS total score (Study 5 in Table 27) 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.

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 4-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 ≥20 at baseline. This double-blind, placebo-controlled trial compared two fixed doses of ABILIFY (10 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 (Study 6 in Table 27).

Table 27: Bipolar Studies

Study Number	Treatment Group	Primary Efficacy Measure: Y-MRS		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
Study 1	ABILIFY (30 / 15 mg/day)*	29.0 (5.9)	-12.52 (1.05)	-5.33 (-7.90, -2.76)
	Placebo	28.5 (4.6)	-7.19 (1.07)	--
Study 2	ABILIFY (30 / 15 mg/day)*	27.8 (5.7)	-8.15 (1.23)	-4.80 (-7.80, -1.80)
	Placebo	29.1 (6.9)	-3.35(1.22)	--
Study 3	ABILIFY (15 - 30 mg/day)*	28.5 (5.6)	-12.64 (0.84)	-3.63 (-5.75 , -1.51)
	Placebo	28.9 (5.9)	9.01 (0.81)	--
Study 4	ABILIFY (15 -30 mg/day)*	28.0 (5.8)	-11.98 (0.80)	-2.28 (-4.44 , -0.11)
	Placebo	28.3 (5.8)	-9.70 (0.83)	--
Study 5	ABILIFY (15 or 30 mg/day)* + Lithium/Valproate	23.2 (5.7)	-13.31 (0.50)	-2.62 (-4.29 , -0.95)
	Placebo + Lithium/Valproate	23.0 (4.9)	-10.70 (0.69)	--
Study 6 (Pediatric, 10-17 years)	ABILIFY (10 mg/day)*	29.8 (6.5)	-14.2 (0.89)	-5.99 (-8.49, -3.50)
	ABILIFY (30 mg/day)*	29.5 (6.3)	-16.5 (0.87)	-8.26 (-10.7, -5.77)
	Placebo	30.7 (6.8)	-8.2 (0.91)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval.
[a] Difference (drug minus placebo) in least-squares mean change from baseline.
* Doses statistically significantly superior to placebo.

Maintenance Treatment of Bipolar I Disorder

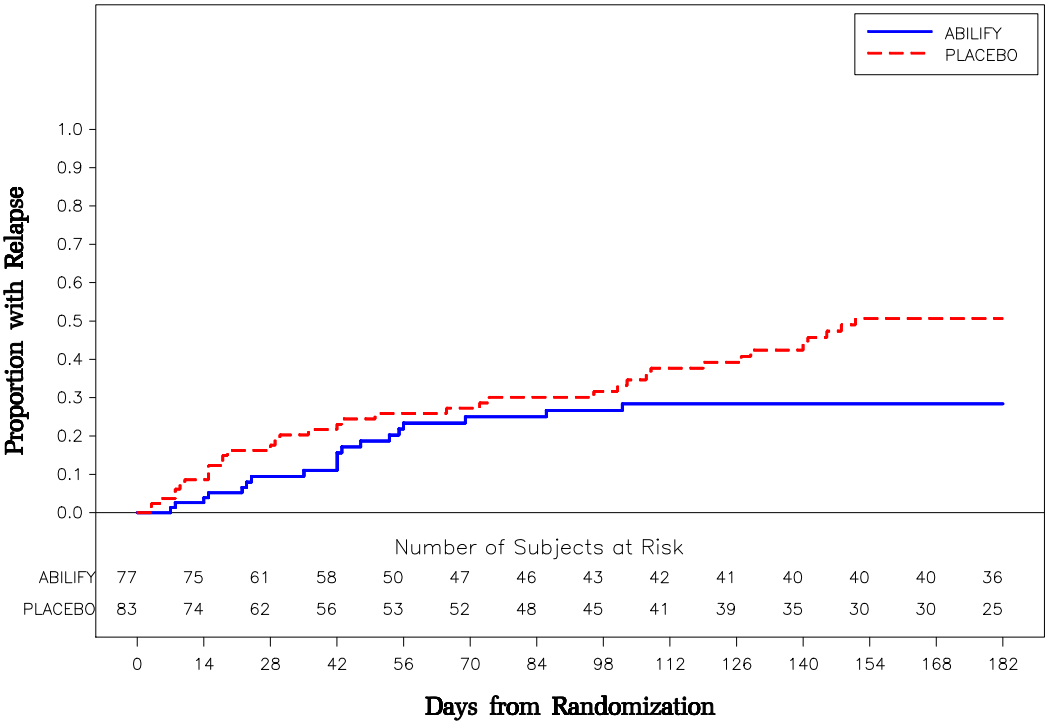
Monotherapy Maintenance Therapy

A maintenance trial was conducted in adult 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 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 (Study 7 in Figure 7). A total of 55 mood events were observed during the double-blind treatment phase. Nineteen were from the ABILIFY group and 36 were from

the placebo group. The number of observed manic episodes in the ABILIFY group (6) were fewer than that in the placebo group (19), while the number of depressive episodes in the ABILIFY group (9) was similar to that in the placebo group (11).

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.

Figure 7: Kaplan-Meier Estimation of Cumulative Proportion of Patients with Relapse (Bipolar Study 7)

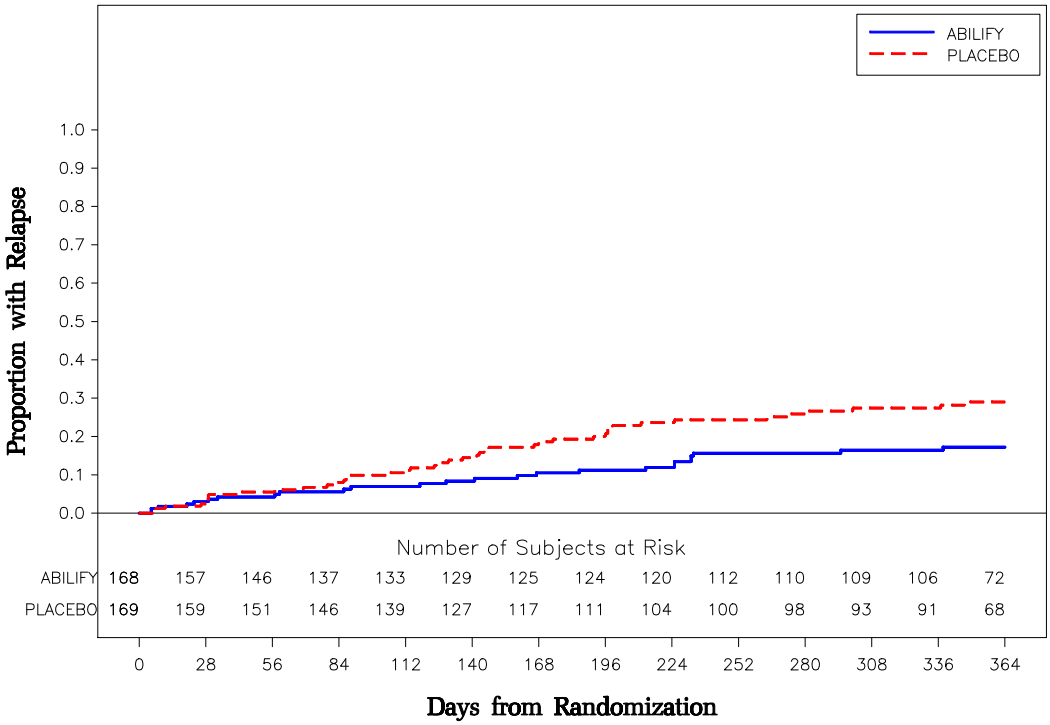


Adjunctive Maintenance Therapy

An adjunctive maintenance trial was conducted in adult patients meeting DSM-IV criteria for bipolar I disorder with a recent manic or mixed episode. Patients were initiated on open-label lithium (0.6 to 1.0 mEq/L) or valproate (50 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 ≥16 and ≤35% improvement on the Y-MRS total score) to lithium or valproate received ABILIFY with a starting dose of 15 mg/day with the option to increase to 30 mg or reduce to 10 mg as early as day 4, as adjunctive therapy with open-label lithium or valproate. Prior to randomization, patients on the combination of single-blind ABILIFY and lithium or valproate were required to

maintain stability (Y-MRS and MADRS total scores ≤12) for 12 consecutive weeks. Three hundred thirty-seven patients were then randomized in a double-blind fashion, to either the same dose of ABILIFY they were on at the end of the stabilization period or placebo plus lithium or valproate and were then monitored for manic, mixed, or depressive relapse for a maximum of 52 weeks. ABILIFY was superior to placebo on the primary endpoint, time from randomization to relapse to any mood event (Study 8 in Figure 8). A mood event was defined as hospitalization for a manic, mixed, or depressive episode, study discontinuation due to lack of efficacy accompanied by Y-MRS score >16 and/or a MADRS >16, or an SAE of worsening disease accompanied by Y-MRS score >16 and/or a MADRS >16. A total of 68 mood events were observed during the double-blind treatment phase. Twenty-five were from the ABILIFY group and 43 were from the placebo group. The number of observed manic episodes in the ABILIFY group (7) were fewer than that in the placebo group (19), while the number of depressive episodes in the ABILIFY group (14) was similar to that in the placebo group (18). The Kaplan-Meier curves of the time from randomization to relapse to any mood event during the 52-week, double-blind treatment phase for ABILIFY and placebo groups are shown in Figure 8.

Figure 8: Kaplan-Meier Estimation of Cumulative Proportion of Patients with Relapse to Any Mood Event (Bipolar Study 8)



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.

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 (HAMD17), minimal HAMD17 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. 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 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 (Studies 1, 2 in Table 28). 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, 5, 10, 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 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.

Table 28: Adjunctive Treatment of Major Depressive Disorder Studies

Study Number	Treatment Group	Primary Efficacy Measure: MADRS		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
Study 1	ABILIFY (5-20 mg/day)* + Antidepressant	25.2(6.2)	-8.49 (0.66)	-2.84 (-4.53 , -1.15)
	Placebo + Antidepressant	27.0 (5.5)	-5.65 (0.64)	--
Study 2	ABILIFY (5-20 mg/day)* + Antidepressant	26.0 (6.0)	-8.78 (0.63)	-3.01 (-4.66 , -1.37)
	Placebo + Antidepressant	26.0 (6.5)	-5.77 (0.67)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval.
[a] Difference (drug minus placebo) in least-squares mean change from baseline.
* Doses statistically significantly superior to placebo.

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 symptoms of irritability in autistic disorder.

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 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 (Study 1 in Table 29).

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 and 15 mg dose arms, and after a third week, it was increased to 15 mg/day in the 15 mg/day treatment arm (Study 2 in Table 29). All three doses of ABILIFY significantly improved scores on the ABC-I subscale compared with placebo.

Table 29: Irritability Associated with Autistic Disorder Studies (Pediatric)

Study Number	Treatment Group	Primary Efficacy Measure: ABC-I		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
Study 1	ABILIFY (2-15 mg/day)*	29.6 (6.37)	-12.9 (1.44)	-7.9 (-11.7, -4.1)
	Placebo	30.2 (6.52)	-5.0 (1.43)	--
Study 2	ABILIFY (5 mg/day)*	28.6 (7.56)	-12.4 (1.36)	-4.0 (-7.7, -0.4)
	ABILIFY (10 mg/day)*	28.2 (7.36)	-13.2 (1.25)	-4.8 (-8.4, -1.3)
	ABILIFY (15 mg/day)*	28.9 (6.41)	-14.4 (1.31)	-6.0 (-9.6, -2.3)
	Placebo	28.0 (6.89)	-8.4 (1.39)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval.
a Difference (drug minus placebo) in least-squares mean change from baseline.
* Doses statistically significantly superior to placebo.

14.5 Tourette's Disorder

Pediatric Patients

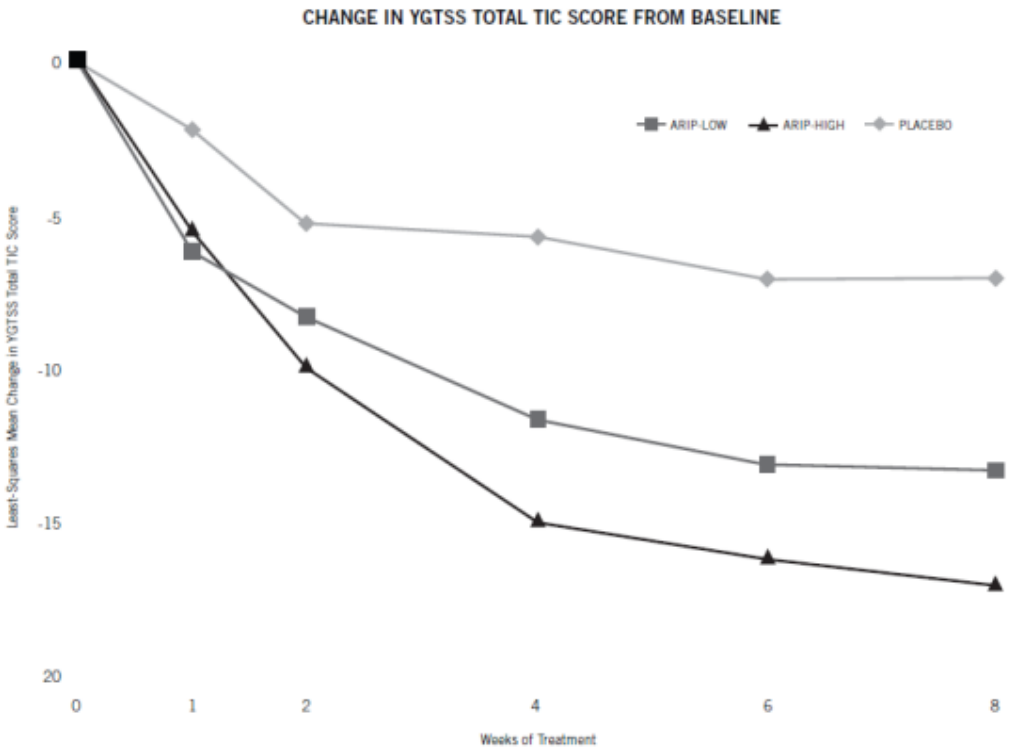
The efficacy of ABILIFY (aripiprazole) in the treatment of Tourette's disorder was established in one 8-week (7 to 17 years of age) and one 10-week (6 to 18 years of age), placebo-controlled trials in pediatric patients (6 to 18 years of age) who met the DSM-IV criteria for Tourette's disorder and had a Total Tic score (TTS) ≥ 20 - 22 on the Yale Global Tic Severity Scale (YGTSS). The YGTSS is a fully validated scale designed to measure current tic severity. Efficacy was evaluated using two assessment scales: 1) the Total Tic score (TTS) of the YGTSS and 2) the Clinical Global Impressions Scale for Tourette's Syndrome (CGI-TS), a clinician-determined summary measure that takes into account all available patient information. Over 65% of these patients were under 13 years of age.

The primary outcome measure in both trials was the change from baseline to endpoint in the TTS of the YGTSS. Ratings for the TTS are made along 5 different dimensions on a scale of 0 to 5 for motor and vocal tics each. Summation of these 10 scores provides a TTS (i.e., 0-50).

The results of these trials are as follows:

In the 8-week, placebo-controlled, fixed-dose trial, children and adolescents with Tourette's disorder (n=133), aged 7 to 17 years, were randomized 1:1:1 to low dose ABILIFY, high dose ABILIFY, or placebo. The target doses for the low and high dose ABILIFY groups were based on weight. Patients < 50 kg in the low dose ABILIFY group started at 2 mg per day with a target dose of 5 mg per day after 2 days. Patients ≥ 50 kg in the low dose ABILIFY group, started at 2 mg per day increased to 5 mg per day after 2 days, with a subsequent increase to a target dose of 10 mg per day at day 7. Patients <50 kg in the high dose ABILIFY group started at 2 mg per day increased to 5 mg per day after 2 days, with a subsequent increase to a target dose of 10 mg per day at day 7. Patients ≥ 50 kg in the high dose ABILIFY group, started at 2 mg per day increased to 5 mg per day after 2 days, with a subsequent increase to a dose of 10 mg per day at day 7 and were allowed weekly increases of 5 mg per day up to a target dose 20 mg per day at Day 21. ABILIFY (both high and low dose groups) demonstrated statistically significantly improved scores on the YGTSS TTS (Study 1 in Table 30) and on the CGI-TS scale compared with placebo. The estimated improvements on the YGTSS TTS over the course of the study are displayed in Figure 9.

Figure 9: Least Square Means of Change from Baseline in YGTSS TTS by Week (Tourette's Disorder Study 1)



In the 10-week, placebo-controlled, flexible-dose trial in children and adolescents with Tourette's disorder (n=61), aged 6 to 18 years, patients received daily doses of placebo or ABILIFY, starting at 2 mg/day with increases allowed up to 20 mg/day based on clinical response. ABILIFY demonstrated statistically significantly improved scores on the YGTSS TTS scale compared with placebo (Study 2 in Table 30). The mean daily dose of ABILIFY at the end of 10-week treatment was 6.54 mg/day.

Table 30: Tourette's Disorder Studies (Pediatric)

Study Number	Treatment Group	Primary Efficacy Measure: YGTSS TTS		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
Study 1	ABILIFY (low dose)*	29.2 (5.63)	-13.4 (1.59)	-6.3 (-10.2, -2.3)
	ABILIFY (high dose)*	31.2 (6.40)	-16.9 (1.61)	-9.9 (-13.8, -5.9)
	Placebo	30.7 (5.95)	-7.1 (1.55)	--
Study 2	ABILIFY (2-20 mg/day)*	28.3 (5.51)	-15.0 (1.51)	-5.3 (-9.8, -0.9)
	Placebo	29.5 (5.60)	-9.6 (1.64)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval.
a Difference (drug minus placebo) in least-squares mean change from baseline.
* Doses statistically significantly superior to placebo.

14.6 Agitation Associated with Schizophrenia or Bipolar Mania

The efficacy of intramuscular ABILIFY 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 ≥15 on the five items comprising the Positive and Negative Syndrome Scale (PANSS) Excited Component (i.e., poor impulse control, tension, hostility, uncooperativeness, and excitement items) with at least two individual item scores ≥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 ABILIFY 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 (Study 1 in Table 31) 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 ABILIFY injection dose of 9.75 mg was evaluated. At 2 hours post-injection, ABILIFY for injection was statistically superior to placebo in the PANSS Excited Component (Study 2 in Table 31) 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 ABILIFY 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 (Study 3 in Table 31).

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

Table 31: Agitation Associated with Schizophrenia or Bipolar Mania Studies

Study Number	Treatment Group	Primary Efficacy Measure: PANSS Excited Component		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
Agitation Associated with Schizophrenia				
Study 1	ABILIFY (1 mg)	19.16 (3.26)	-4.47 (0.72)	-1.19 (-2.96 , 0.59)
	ABILIFY (5.25 mg)*	19.41 (3.31)	-5.65 (0.68)	-2.37 (-4.10 , -0.63)
	ABILIFY (9.75 mg)*	19.42 (2.80)	-6.69 (0.72)	-3.40 (-5.18 , -1.62)
	ABILIFY (15 mg)*	19.34 (2.38)	-5.72 (0.72)	-2.44 (-4.21 , -0.68)
	Placebo	19.18 (2.95)	-3.28 (0.70)	--
Study 2	ABILIFY (9.75 mg)*	18.82 (2.67)	-7.27 (0.59)	-2.48 (-3.77, -1.19)
	Placebo	18.74 (2.71)	-4.78 (0.69)	--
Agitation Associated with Bipolar Mania				
Study 3	ABILIFY (9.75 mg)*	18.77 (2.45)	-8.74 (0.57)	-2.99 (-4.53, -1.44)
	ABILIFY (15 mg)*	18.29 (2.49)	-8.67 (0.57)	-2.91 (-4.44, -1.38)
	Placebo	17.95 (2.63)	-5.76 (0.58)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval.
[a] Difference (drug minus placebo) in least-squares mean change from baseline.
* Doses statistically significantly superior to placebo.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

ABILIFY® (aripiprazole) Tablets have markings on one side and are available in the strengths and packages listed in Table 32.

Table 32: ABILIFY Tablet Presentations

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

ABILIFY DISCMELT® (aripiprazole) Orally Disintegrating Tablets are round tablets with markings on either side. ABILIFY DISCMELT is available in the strengths and packages listed in Table 33.

Table 33: ABILIFY DISCMELT Orally Disintegrating Tablet Presentations

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

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

150 mL bottle NDC 59148-013-15

ABILIFY® (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 25ºC (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

Discuss the following issues with patients prescribed ABILIFY:

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 including information 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 ABILIFY 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 ABILIFY therapy does not affect them adversely *[see WARNINGS AND PRECAUTIONS (5.9)]*.

Nursing

Advise patients that breastfeeding is not recommended with ABILIFY treatment because of the potential for serious adverse reactions in a nursing infant *[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)]*.

Heat Exposure and Dehydration

Patients should be advised regarding appropriate care in avoiding overheating and dehydration *[see WARNINGS AND PRECAUTIONS (5.10)]*.

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

ABILIFY is a trademark of Otsuka Pharmaceutical Company.

03US14L-1121 Rev December 2014

MEDICATION GUIDE

ABILIFY® (a BIL ĭ fī)
(aripiprazole)
Tablets

ABILIFY® (a BIL ĭ fī)
(aripiprazole)
Orally Disintegrating Tablets

ABILIFY® (a BIL ĭ fī)
(aripiprazole)
Oral Solution

ABILIFY® (a BIL ĭ fī)
(aripiprazole)
Injection, for intramuscular use

Read this Medication Guide before you start taking ABILIFY and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is the most important information I should know about ABILIFY?

(For other side effects, also see "**What are the possible side effects of ABILIFY?**").

Serious side effects may happen when you take ABILIFY, including:

- **Increased risk of death in elderly patients with dementia-related psychosis:** Medicines like ABILIFY can raise the risk of death in elderly people who have lost touch with reality (psychosis) due to confusion and memory loss (dementia). ABILIFY is not approved for the treatment of patients with dementia-related psychosis.
- **Risk of suicidal thoughts or actions:** 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.

What is ABILIFY?

- **ABILIFY Oral Tablets, Orally-Disintegrating Tablets, and Oral Solution** are prescription medicines used to treat:
  - Schizophrenia
  - manic or mixed episodes that happen with bipolar I disorder
  - major depressive disorder (MDD) when ABILIFY is used with antidepressant medicines
  - irritability associated with autistic disorder
  - Tourette's disorder
- **ABILIFY Injection** is a prescription medicine used to treat:
  - agitation associated with schizophrenia or bipolar mania

It is not known if ABILIFY is safe or effective in children:

- under 13 years of age with schizophrenia
- under 10 years of age with bipolar I disorder
- under 6 years of age with irritability associated with autistic disorder
- under 6 years of age with Tourette's disorder

Who should not take ABILIFY?

Do not take ABILIFY if you are allergic to aripiprazole or any of the ingredients in ABILIFY. See the end of this Medication Guide for a complete list of ingredients in ABILIFY.

What should I tell my healthcare provider before taking ABILIFY?

Before taking ABILIFY, tell your healthcare provider if you have or had:

- diabetes or high blood sugar in you or your family; your healthcare provider should check your blood sugar before you start ABILIFY and also during therapy.
- seizures (convulsions).
- low or high blood pressure.
- heart problems or stroke.
- pregnancy or plans to become pregnant. It is not known if ABILIFY will harm your unborn baby.
- breast-feeding or plans to breast-feed. ABILIFY can pass into your breast milk and may harm your baby. Talk to your healthcare provider about the best way to feed your baby if you receive ABILIFY.
- low white blood cell count.
- phenylketonuria. ABILIFY DISCMELT Orally Disintegrating Tablets contain phenylalanine.
- any other medical conditions.

Tell your healthcare provider about all the medicines that you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

ABILIFY and other medicines may affect each other causing possible serious side effects. ABILIFY may affect the way other medicines work, and other medicines may affect how ABILIFY works.

Your healthcare provider can tell you if it is safe to take ABILIFY with your other medicines. Do not start or stop any medicines while taking ABILIFY without talking to your healthcare provider first. Know the medicines you take. Keep a list of your medicines to show your healthcare provider and pharmacist when you get a new medicine.

How should I take ABILIFY?

- Take ABILIFY exactly as your healthcare provider tells you to take it. Do not change the dose or stop taking ABILIFY yourself.
- ABILIFY can be taken with or without food.
- ABILIFY tablets should be swallowed whole.
- If you miss a dose of ABILIFY, take the missed dose as soon as you remember. If it is almost time for the next dose, just skip the missed dose and take your next dose at the regular time. Do not take two doses of ABILIFY at the same time.
- If you have been prescribed ABILIFY DISCMELT, take it as follows:
  - Do not open the blister until ready to take the DISCMELT tablet.
  - To remove one DISCMELT tablet, 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 DISCMELT tablet.
- If you take too much ABILIFY, call your healthcare provider or poison control center at 1-800-222-1222 right away, or go to the nearest hospital emergency room.

What should I avoid while taking ABILIFY?

- Do not drive, operate heavy machinery, or do other dangerous activities until you know how ABILIFY affects you. ABILIFY may make you drowsy.
- Avoid getting over-heated or dehydrated.
  - Do not over-exercise.
  - In hot weather, stay inside in a cool place if possible.
  - Stay out of the sun. Do not wear too much or heavy clothing.
  - Drink plenty of water.

What are the possible side effects of ABILIFY?

ABILIFY may cause serious side effects, including:

- **See "What is the most important information I should know about ABILIFY?"**
- **Stroke in elderly people (cerebrovascular problems) that can lead to death**
- **Neuroleptic malignant syndrome (NMS).** Tell your healthcare provider right away if you have some or all of the following symptoms: high fever, stiff muscles, confusion, sweating, changes in pulse, heart rate, and blood pressure. These may be symptoms of a rare and serious condition that can lead to death. Call your healthcare provider right away if you have any of these symptoms.
- **Uncontrolled body movements (tardive dyskinesia).** ABILIFY may cause movements that you cannot control in your face, tongue, or other body parts. Tardive dyskinesia may not go away, even if you stop receiving ABILIFY. Tardive dyskinesia may also start after you stop receiving ABILIFY.
- **Problems with your metabolism such as:**
  - **high blood sugar (hyperglycemia) and diabetes.** Increases in blood sugar can happen in some people who take ABILIFY. Extremely high blood sugar can lead to coma or death. If you have diabetes or risk factors for diabetes (such as being overweight or a family history of diabetes), your healthcare provider should check your blood sugar before you start ABILIFY and during your treatment.

    Call your healthcare provider if you have any of these symptoms of high blood sugar while receiving ABILIFY:

    - feel very thirsty
    - need to urinate more than usual
    - feel very hungry
    - feel weak or tired
    - feel sick to your stomach
    - feel confused, or your breath smells fruity

- **increased fat levels (cholesterol and triglycerides) in your blood.**
- **weight gain.** You and your healthcare provider should check your weight regularly.

- **Orthostatic hypotension (decreased blood pressure).** Lightheadedness or fainting may happen when rising too quickly from a sitting or lying position.
- **Low white blood cell count**
- **Seizures (convulsions)**
- **problems with control of your body temperature especially when you exercise a lot or are in an area that is very hot. It is important for you to drink water to avoid dehydration.** See "What should I avoid while receiving ABILIFY?"
- **difficulty swallowing that can cause food or liquid to get into your lungs.**

The most common side effects of ABILIFY in adults include:

- nausea
- vomiting
- constipation
- headache
- blurred vision
- upper respiratory illness
- dizziness
- anxiety
- insomnia
- restlessness
- inner sense of restlessness/need to move (akathisia)

The most common side effects of ABILIFY in children include:

- feeling sleepy
- headache
- vomiting
- fatigue
- increased or decreased appetite
- increased saliva or drooling
- insomnia
- nausea
- stuffy nose
- weight gain
- uncontrolled movement such as restlessness, tremor, muscle stiffness

These are not all the possible side effects of ABILIFY. For more information, ask your healthcare provider or pharmacist.

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

How should I store ABILIFY?

- Store ABILIFY at room temperature, between 68°F to 77°F (20°C to 25°C).
- 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.

Keep ABILIFY and all medicines out of the reach of children.

General information about the safe and effective use of ABILIFY.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ABILIFY for a condition for which it was not prescribed. Do not give ABILIFY to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about ABILIFY. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about ABILIFY that was written for healthcare professionals.

For more information about ABILIFY visit www.abilify.com.

What are the ingredients in ABILIFY?

Active ingredient: aripiprazole

Inactive ingredients:

Tablets: 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: acesulfame potassium, aspartame (which contains phenylalanine), 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: disodium edetate, fructose (200 mg per mL), glycerin, dl-lactic acid, methylparaben, propylene glycol, propylparaben, sodium hydroxide, sucrose (400 mg per mL), and purified water. The oral solution is flavored with natural orange cream and other natural flavors

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

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

ABILIFY is a trademark of Otsuka Pharmaceutical Company.

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Otsuka America Pharmaceutical, Inc.

Revised: December 2014

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/s/

MITCHELL V Mathis
12/12/2014

EXHIBIT B

6/15/05

Food and Drug Administration
Office of Orphan Products Development (HF-35)
5600 Fishers Lane
Rockville, MD 20857
(301) 827-3666
FAX: (301) 443-4915

APPLICATION FOR ORPHAN DRUG DESIGNATION

(1) Floyd R. Sallee, M.D., Ph.D. requests orphan drug designation for aripiprazole, 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl] butoxy]-3,4-dihydrocarbostyril for the treatment of Tourette Syndrome in children and adolescents.

(2): Sponsor: Floyd R. Sallee, M.D., Ph.D.

Contact: Floyd R. Sallee, M.D., Ph.D.
University of Cincinnati School of Medicine
231 Albert Sabin Way
Cincinnati, OH 45267-0559

Phone: (513) 558-8663

Chemical Name: 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl] butoxy]-3,4-dihydrocarbostyril

Generic Name: Aripiprazole

Trade Name: Abilify™

Drug Source: Otsuka America Pharmaceutical, Inc., Rockville MD, GMP manufactured 5 and 10 mg tablets.

(3) Description of the rare disease for which the drug is being investigated, the proposed indication and reason why therapy is needed.

Rare Disease: Tourette Syndrome in children and adolescents.

Description

Tourette's syndrome (TS) is a childhood-onset disorder characterized by motor and vocal tics which tend to lessen in severity as development progresses. Although for most cases tics are mild (and often untreated), for 1/3 of identified cases symptoms are more severe and disabling, causing both social and academic impairment such that medication therapy is needed. It is this latter group which this application is directly meant to address. Though the Diagnostic and Statistical Manual of Mental Disorders, IV is the principal guide for diagnostic recognition and classification, symptom severity and impairment are often used to define subclassfications likely to be medicated (Robertson 2003).

Prevalence rates for TS are highest in school-age children, with frequency considerably reduced in adolescents and adults. The most comprehensive epidemiologic study conducted in a younger population was that of Apter et al. (1993) who conducted an epidemiologic survey of Israeli army recruits ages 16-17. The Apter study found a **point prevalence of 4.3 +/- 1.2 (mean +/- SE) per 10,000 with the 95% confidence interval for this estimate at 1.9 to 6.7 per 10,000.** The most widely held estimate of prevalence in school age children comes from a review of 6 studies in several Western developed countries in which Mary Robertson (2003) concluded that a realistic estimate of the prevalence of TS is around 1% for a school age population. Harvey Singer in a more recent comprehensive review (2005) estimates the prevalence of TS at around one to ten in 1000 children, or to range between 0.1% to 1%.

Singer (2005) also emphasizes that the population most likely to be treated for TS is school aged (ages 6-17), with severities of at least a moderate level, which represents about 1/3 of those identified or diagnosed in clinical populations. Recent US Census figures (Estimates of the Resident Population by Selected Age Groups for the United States and States and for Puerto Rico: July 1, 2004 (SC-EST2004-01RES) indicate the US school age population is currently 36 million. Using the most recent prevalence estimate of 0.1% to 1%, the US TS population is in the range of 36,000 to 360,000 school aged children. Of whom, about 33% experience the more pronounced and severe symptoms (Robertson 2003) such that clinical treatment is both warranted and likely to occur. Thus a conservative estimate of the **target TS population in US school age children is 120,000, fewer than 200,000 prevalence in the US.**

Need for TS therapies with better risk/benefit

There are currently four drugs granted orphan status designations for the treatment of Tourette Syndrome. These are a norepinephrine reuptake inhibitor, atomoxetine on 8/26/2003, a nicotinic receptor antagonist, mecamylamine on 10/14/1998, a dopamine agonist, pergolide on 11/20/1997, and a selective dopamine D2 blocker, tiapride on 11/4/1998. As sponsor of the pergolide designation, it has become apparent that none of these so designated pharmacologic mechanisms of action are likely to achieve comparable clinical efficacy and safety to the more widely used drug class of atypical antipsychotics. Aripiprazole, a member of the atypical antipsychotic drug class, is the proposed candidate for such orphan drug designation.

The modern view of TS is as a disturbance of brain neurochemical function. In addition to the pharmacologic evidence of tic suppression by dopamine receptor blockade, several lines of evidence converge to implicate a state of postsynaptic DA

receptor supersensitivity underlying TS (Singer 2005). Dr. Singer and colleagues (1982) were the first to describe that cerebrospinal fluid levels of the major DA metabolite homovanillic acid (HVA) were reduced in TS patients, suggesting that the findings of excessive DA activity in the condition are not due to increased release or turnover of the neurotransmitter, but rather implicated postsynaptic receptor supersensitivity (i.e., increased receptor number or affinity). Although some recent information may be inconsistent, this notion of DA receptor supersensitivity as the primary pathogenetic mechanism of tics has been widely held for nearly three decades and has guided medication therapy.

Old Treatments

Classical neuroleptic antipsychotic drugs (e.g. haloperidol and pimozide), which are potent antagonists of DA D2 receptors, have been the mainstay of pharmacotherapy for tics. The tic-suppressing effect of classical antipsychotics has been well-established for a number of such drugs, particularly pimozide, in several clinical trials (Kurlan & Trinidad, 1995). This class of medications has been the most predictably effective in suppressing tics, but its use is limited by a variety of acute and chronic side effects, including sedation, dysphoria, phobias, weight gain, parkinsonism, akathisia and others. Haloperidol (Haldol®) is the longest used and best studied medication for TS. It has been considered the standard medication for treating TS for more than 3 decades as its tic suppressing effects have been established in a number of clinical trials (Kurlan & Trinidad, 1995).

Of the classical antipsychotics, pimozide (Orap®) is the only one with an FDA-approved indication for TS. Pimozide has been studied in TS in a multicenter trial by the Tourette Syndrome Study Group (1999) and in a single center by Sallee and colleagues (1997). Of the neuroleptics, this drug in particular has a tendency to prolong cardiac repolarization which has been associated with a specific and potentially life-threatening ventricular tachycardia termed “torsades de pointes”. This type of arrhythmia is usually seen in the setting of drug-induced prolongation of the Q-T interval on the ECG. This potential cardiotoxicity is highlighted by the recent FDA warning that the combined use of pimozide with the SSRI sertraline (Zoloft®) is contraindicated due to observed elevations of pimozide blood levels and possible increased risk of cardiac effects. Although not specifically mentioned by the FDA, the same potential risks would exist if pimozide is combined with other SSRIs, particularly those that are inhibitors of CYP3A4 microsomal enzymes (e.g., fluoxetine, fluvoxamine, nefazadone). This drug interaction issue is particularly relevant to the treatment of TS patients since they often need both a tic suppressant and an anti-OCD (usually an SSRI) drug. Because of the cardiac influences, pimozide has been relegated to “second line” status by the FDA, meaning it should not be prescribed to patients unless they have failed other neuroleptic drugs.

New Treatments

The limited tolerability of classical neuroleptics has led to interest in the so-called “atypical” antipsychotics for treating TS. All atypical antipsychotics are characterized by having a relatively greater affinity for 5-HT2 receptors than for D2 receptors, so they may be less potent tic suppressors than the classical neuroleptics. When studied in psychotic psychiatric patients, these newer agents (risperidone, clozapine, olanzapine,

quetiapine, ziprasidone, aripiprazole) have been reported to have a better side effect profile, particularly inducing fewer extrapyramidal motor effects, than the classical types.

The general conclusions in comparative studies of the two antipsychotic classes is that there is comparable efficacy and that the atypicals have a better side effect profile (particularly related to extrapyramidal side effects) except for a possibly increased frequency of weight gain. There have been recent concerns about an increased risk of diabetes mellitus in patients receiving atypical antipsychotics. The risk appears to be low. In an industry clinical trials database (Eli Lilly and Co, written communication, 2/03), the incidence of diabetes in subjects taking risperidone was only 0.6%, compared to 0.4% for haloperidol. The manufacturer of risperidone (Risperdal®), Janssen Pharmaceutica, Inc. added a new warning to its package insert for the drug in April, 2003 regarding a possible increased risk of cerebrovascular events, including stroke. This warning was based on data from 4 placebo-controlled trials of the drug being conducted in elderly, demented subjects. To date, no substantial increased risk of cerebrovascular side effects has been reported in other patient populations.

Dehning et al. (2005) recently published a case report of a TS patient treated successfully with aripiprazole, while Kastrup et al. (2005) present two cases of TS producing complete resolution of TS symptoms. Stigler et al. (2004) present five cases of positive clinical response to aripiprazole in youths with pervasive developmental disorder (PDD) and no significant adverse effects. These preliminary reports argue for a more detailed series of studies aimed at an indication in TS, and justify this request of Orphan Designation for Aripiprazole.

(4a) Clinical/Preclinical Pharmacology of aripiprazole, 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl] butoxy]-3,4-dihydrocarbostyril

Overview

Aripiprazole exhibits excellent affinity for dopamine D2 and D3 receptors, serotonin 5-HT1A and 5-HT2A receptors, moderate affinity for dopamine D4, serotonin 5-HT2C and 5-HT7, alpha1-adrenergic and histamine H1 receptors, and moderate affinity for the serotonin reuptake sites. There is no appreciable affinity for cholinergic muscarinic receptors. It is proposed that aripiprazole's effect in the management of schizophrenia and bipolar disorder is related to a partial agonist activity at the D2 and 5-HT1A receptors and antagonist activity at the 5-HT2A receptors. Aripiprazole's side effect profile of limited orthostatic hypotension is likely mediated by antagonist activity of the alpha1-adrenergic receptors (Abilify package insert).

Mode of Action

Aripiprazole's unique agonist/antagonist action at dopamine receptors separates it from the field of atypical agents currently in use to treat TS. As a partial agonist of the D2, D3, 5-HT1A and 5-HT2A receptors, aripiprazole may well reduce the propensity of tics in TS which are thought to be due to the post-synaptic receptor supersensitivity as proposed by Dr. Singer and colleagues (1982).

Nonclinical General Pharmacology

Aripiprazole partial agonist activity action on prolactin release and cAMP levels has been studied in the retrovirally transduced Human D2 receptor modified rate pituitary cell line known as GH4C1. Aripiprazole competitively inhibited DA binding while mediating the hyperprolactinemia that should result from a complete DA inhibitor. The reduced propensity for hyperprolactinemia is postulated to be due to a direct antagonist activity at the D2L pituitary isoform in the post-synaptic pituitary tissue, and a direct agonist activity at the D2S pituitary isoform in the pre-synaptic dopamine autoreceptors in pituitary tissue (Aihara et al. 2004).

Aripiprazole exhibits partial agonist activity at 5-HT1A receptors and antagonist activity at 5-HT2A receptors. This has led to the suggestion that aripiprazole is the first dopamine-serotonin system stabilizer, which may be a better term than second generation antipsychotic (Aihara et al. 2004). The 5-HT1A agonist activity as studied in Chinese hamster ovary cell membranes supports similar findings of attenuated prolactin release and a high affinity, potent, partial agonist activity at the 5-HT1A receptor. The 5-HT2A receptor antagonist activity has been observed, which supports the dopamine-serotonin system stabilization theory (Jordan et al., 2002).

Toxicology

Animal carcinogenicity studies performed in rodents at .2 to 19 times the maximum recommended human dose (MRHD) of Abilify demonstrated no development of tumors in male rodents, however, mammary gland adenocarcinomas and adenocanthomas, mammary gland fibroadenomas, and adrenocortical carcinomas were present at increased incidence in female rodents. Similar tumors in other rodent studies using other antipsychotics are thought to be prolactin-mediated. While prolactin levels were not measured in the aripiprazole carcinogenicity studies, elevated serum prolactin levels were found in a separate study that administered aripiprazole at doses associated with tumor development (Abilify package insert).

Four *in vitro* assays and one *in vivo* assay were performed to measure the mutagenic potential of aripiprazole. The results from one *in vitro* assay demonstrated that aripiprazole and a metabolite were clastogenic in an assay performed on Chinese hamster lung (CHL) cells. A positive clastogenic response was also obtained from the *in vivo* assay but the mechanism of action is not considered relevant for humans (Abilify package insert).

Animal fertility studies demonstrated no overall fertility impairment in female or male rats. Some irregularities were apparent after treatments beyond the MRHD. Female rats treated with doses .6 to 6 times the MRHD showed increased corpora lutea and estrus cycle irregularities. Male rats treated with doses 6 to 19 times the MRHD demonstrated spermatogenesis irregularities and prostate atrophy (Abilify package insert).

Aripiprazole has little toxic information available for pediatric dosing and pharmacokinetic profile, with anecdotal information on accidental ingestion (Schonberger et al. 2004). The reported peak serum concentration of 136 micrograms per liter is within the normal adult therapeutic steady state range of 98-452 micrograms per liter. Other reported accidental ingestions have resulted in no apparent incident at adult therapeutic levels but have noted central nervous system depression and mild tachycardia

in one 2.5 year old who ingested 225mg. Other adverse effect has been reported in an adolescent who had previous history of similar symptoms (Lindsey et al. 2003).

Clinical Studies

Efficacy for Schizophrenia and Bipolar Disorder has been established in several placebo-controlled clinical trials for each indication. No clinical studies have yet to be systematically undertaken to determine efficacy in TS. Efficacy for schizophrenia was established in two studies for each of the following doses: 15 mg, 20 mg, and 30 mg. At 10 mg efficacy was established in one study. The measures used for clinical outcomes were several subscales of the Positive and Negative Syndrome Scale (PANSS), and the Clinical Global Impression (CGI) (Abilify package insert).

As described in a comprehensive review, DeLeon et al. (2004) indicated that there are only two published studies on the efficacy of treatment of schizophrenia and schizoaffective disorder with aripiprazole. One study was a multi-center, double-blind, placebo-controlled study with 414 study participants (SPs) with either schizophrenia or schizoaffective disorder. The SPs were assigned to one of four treatment arms: 1. aripiprazole 15 mg/d (n=102), 2. aripiprazole 30 mg/d (n=102), 3. haloperidol 10 mg/d (n=104) or 4. placebo (n=106). The primary efficacy measures utilized were the PANSS, a PANSS subscale (positive), and the Clinical Global Impressions Severity of Illness (CGI-S). Results measured include the following: PANSS total: for all (treatment groups) vs. placebo, $p \leq 0.009$; PANSS positive: for all vs. placebo $p \leq 0.001$; CGI-S: for all vs. placebo $p \leq 0.019$ (Kane et al. 2002).

The second published study on efficacy with schizophrenia and schizoaffective disorder described by DeLeon et al. (2004) was a Phase III, inpatient, 4-week, double-blind, randomized placebo-controlled, parallel-group study with 404 SPs. The four treatment arms included: 1. aripiprazole 20 mg/d (n=101), 2. aripiprazole 30 mg/d (n=101), 3. risperidone 6 mg/d (n=99), or placebo (n=103). Efficacy measures included were the PANSS, PANSS positive, and the (CGI-S). Results included the following: PANSS total: for all (treatment groups) vs. placebo, $p \leq 0.003$; PANSS positive: for all vs. placebo $p \leq 0.02$; CGI-S: for all vs. placebo $p \leq 0.03$ (Potkin et al. 2003).

Efficacy for bipolar disorder with acute mania as presented in the Abilify package insert was established with two three-week placebo-controlled studies (n=268; n=248). These two inpatient studies involved participants that met criteria for Bipolar 1 with manic or mixed episodes. The primary efficacy measures were the Young Mania Rating Scale (Y-MRS) and the Clinical Global Impression – Bipolar (CGI-BP) scale for outcome measures. The doses were tested at 15 and 30 mg. A review of the literature resulted in one published controlled trial of aripiprazole and the treatment of Bipolar disorder, which is also described in the comprehensive review by DeLeon et al. (2004). This trial was a Phase III randomized, placebo-controlled with 262 SPs randomized to one of the following treatment arms for three weeks: 1. aripiprazole 30 mg. (reduced to 15 mg/d as needed), or 2. placebo. The primary efficacy measure was the mean change in total score of the Young-Mania Rating Scale (Y-MRS) with a response indicated by a $\geq$ 50% decrease in score. Results for the Y-MRS aripiprazole vs. placebo, $p = 0.002$ (Keck et al. 2003).

Other clinical symptoms of second generation antipsychotic (SGA) therapy, namely QTc alteration seems to be markedly different with aripiprazole. Many

antipsychotics in immediate or prolonged use may lengthen the QT interval which prolongs the repolarization period and increases the likelihood of torsades de pointes and sudden death. Aripiprazole has been reported to reduce the QTc which in turn reduces the risk of the deadly torsades de pointes (Goodnick et al., 2002).

(4B) Scientific Rationale for Aripiprazole Treatment of Tourette Syndrome in Children and Adolescents

We believe aripiprazole will prove a safe and efficacious treatment for TS for several reasons; 1) its unique pharmacodynamic action as a dopamine agonist/antagonist, 2) its optimum safety profile in adult indications even in the presence of concomitant treatments, 3) its safety and tolerability in small studies involving aggressive youth with pervasive developmental disorder.

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Estimates of the Resident Population by Selected Age Groups for the United States and States and for Puerto Rico: July 1, 2004 (SC-EST2004-01RES)

(5) No drug has marketing approval for the claimed designation.

(6) The subset of persons suffering from TS, namely children and adolescents with moderate to severe tic symptoms which would, under clinically accepted practices (see Singer 2005), be treated with pharmacotherapy. As the population most likely to be treated for TS is school aged (ages 6-17), with severities of at least a moderate level, which represents about 1/3 of those identified or diagnosed in clinical populations (Singer 2005).

(7) Otsuka Pharmaceutical Co., LTD., has current FDA marketing approval for the treatment of schizophrenia and bipolar disorder under NDA 21-436.

(8i) Prevalence rates for TS are highest in school-age children, with frequency considerably reduced in adolescents and adults. Apter et al. (1993) conducted an epidemiologic survey of Israeli army recruits ages 16-17, and found a **point prevalence of 4.3 +/- 1.2 (mean +/- SE) per 10,000 with the 95% confidence interval for this estimate at 1.9 to 6.7 per 10,000.** After a review of six studies with school age children in several Western developed countries Mary Robertson (1993) concluded that a realistic estimate of the prevalence of TS is around 1% for a school age population. Harvey Singer in a more recent comprehensive review (2005) estimates the prevalence of TS at around one to ten in 1000 children, or to range between 0.1% to 1%.
Recent US Census figures (Estimates of the Resident Population by Selected Age Groups for the United States and States and for Puerto Rico: July 1, 2004 (SC-EST2004-01RES) indicate the US school age population is currently 36 million. Using the most recent prevalence estimate of 0.1% to 1%, the US TS population is in the range of 36,000 to 360,000 school aged children. Of whom, about 33% experience the more pronounced and severe symptoms (Robertson 2003) such that clinical treatment is both warranted and likely to occur. Thus a conservative estimate of the **target TS population in US school age children is 120,000, fewer than 200,000 prevalence in the US.**

(9) The sponsor of this application is not the real party of interest for developing and manufacturing the drug. The real party of interest for developing and manufacturing the drug is Otsuka America Pharmaceutical, Inc., Rockville MD.

Sincerely,

Floyd R. Sallee, M.D., Ph.D.

EXHIBIT C

Otsuka

Otsuka-people creating new products for better health worldwide

Mitchell V. Mathis, M.D., CAPT, USPHS
Director (Acting)
Division of Psychiatry Drug Products, HFD-130
Center for Drug Evaluation and Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, Maryland 20705-1266

Attn: **DOCUMENT CONTROL ROOM**

NDA 21-436 [Sequence # 0045]
Aripiprazole (OPC-14597/Abilify®) Tablets
Supplemental New Drug Application (sNDA),
Treatment of tics associated with Tourette's disorder

Dear Dr. Mathis:

Reference is made to Otsuka Pharmaceutical Company Ltd.'s (OPC) approved New Drug Application, NDA 21-436, for Aripiprazole (OPC-14597) Oral Tablets which was approved on November 15, 2002. Further reference is made to IND 116,003 for Aripiprazole Oral Tablets (treatment of tics associated with Tourette's disorder in children and adolescents) submitted on August 15, 2012.

Pursuant to 21 CFR 314.70, Otsuka is hereby submitting a supplemental new drug application (sNDA) requesting approval to add a new indication, treatment of tics associated with Tourette's disorder in pediatric patients (6-17 years), to the labeling for this product. Tourette's disorder is a rare condition primarily affecting children and adolescents. An orphan drug designation application was submitted to the Office of Orphan Product Development on June 25, 2005, and orphan drug designation for the treatment of Tourette's disorder in children and adolescents was granted on January 25, 2006 (designation no. 05-2079).

The primary evidence for the safety and efficacy of aripiprazole for this indication is provided by the results of the following 2 pivotal placebo-controlled trials included in this application:

> **Trial 31-12-293**: A Multicenter, Randomized, Double-blind, Placebo-controlled Study Evaluating the Safety and Efficacy of Fixed-dose Once-daily Oral Aripiprazole in Children and Adolescents with Tourette's Disorder

Otsuka Pharmaceutical Development & Commercialization, Inc.
2440 Research Boulevard ● Rockville, Maryland 20850 ● Phone: 301-417-0900 ● Fax: 301-990-0036 ● www.otuska-us.com

Trial 031-KOA-0703: A Randomized, Double-bind, Dose-adjustment, Placebo-controlled Study to Evaluate the Efficacy and Safety of Aripiprazole in Children and Adolescents with Chronic Tic Disorders or Tourette's Disorder

The safety of aripiprazole for the Tourette's indication is further supported by data from an ongoing, long-term, open-label trial in Tourette's disorder (Trial 31-12-294) and the aggregate clinical trial and post-marketing safety experience in children and adolescents across the various other indications for which aripiprazole has previously been approved for use in the pediatric population, including schizophrenia, bipolar disorder I, and autistic disorder. The aggregate safety data included in this submission includes 959 pediatric subjects exposed to aripiprazole for at least 180 days, and 556 pediatric subjects exposed for at least 360 days in clinical trials (Tourette's disorder, schizophrenia, bipolar disorder I, and autistic disorder).

Please note the following:

A reviewer's guide is provided in Module 1.2, Reviewers Guide.

Otsuka believes that aripiprazole for the treatment of Tourette's disorder meets FDA's criteria for priority review, and therefore respectfully requests that this sNDA be assigned a priority review classification as outlined in the justification located in the reviewer's guide.

Pediatric Information - Tourette's disorder is a neuropsychiatric disorder with childhood onset that primarily affects children and adolescents; therefore, this sNDA is based entirely on studies conducted in the pediatric population, ages 6-17. Aripiprazole for the Tourette's indication is an orphan drug and in accordance with 21 CFR 314.55(d), it is therefore exempt from the requirement to submit pediatric data or request a waiver or deferral for all pediatric subpopulations. Accordingly, a request for a waiver or deferral for children less than 6 years of age is not needed for this application. In addition, as confirmed in the e-mail correspondence from Kofi Ansah of FDA to Patrick Guinn (Module 1.12.4, Request for clarification, e-mail dated October 17, 2013), a Pediatric Study Plan (PSP) is not needed for this supplemental application based on the exemption from the pediatric requirements under PREA cited above.

The requirements for an Integrated Summary of Safety (ISS) and Integrated Summary of Effectiveness (ISE) have been addressed by including the applicable summaries and analyses within the Summary of Clinical Efficacy (SCE – Section 2.7.3) and the Summary of Clinical Safety (SCS – Section 2.7.4), respectively. A separate ISE and ISS are not included in this sNDA as per the pre-sNDA Meeting email correspondence from Kofi Ansah to Patrick Guinn (Module 1.6.3, e-mail dated May 21 and Module 1.6.3, e-mail dated May 23, 2013), where FDA stated that information from the ISS should be placed in the SCS in Module 2 and the ISS should be removed from Module 5 to eliminate redundancy. FDA also accepted Otsuka's proposal to provide information from the ISE in the SCE in Module 2 and to remove the ISE from Module 5 to eliminate redundancy.

Reference is made to NDA 21-436 for Chemistry, Manufacturing, and Controls (CMC) information for aripirazole oral tablets. No new CMC information is included in this sNDA as per the pre-sNDA Meeting email correspondence from Kofi Ansah to Patrick Guinn (Module 1.6.3, e-mail dated May 21, 2013), where FDA agreed that the requirements for CMC information could be satisfied by cross-referencing the current approved NDA.

Reference is made to NDA 21-436 for information on nonclinical studies with orally administered aripiprazole. No new nonclinical study reports are included in this sNDA as per the pre-sNDA Meeting email correspondence from Kofi Ansah to Patrick Guinn (Module 1.6.3, e-mail dated May 21, 2013), where FDA agreed that no new nonclinical reports are required for this sNDA.

Claim for Exclusivity

As noted above, aripiprazole for the treatment of Tourette's disorder indication is an Orphan Drug (Orphan Designation granted January 25, 2006, no. 05-2079), and is therefore entitled to receive 7 years of orphan exclusivity in accordance with 21 CFR 316.31(a). See Module 1.3.5.3, Exclusivity Request.

In accordance with Section 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act, and FDA's September 2011 Guidance for Industry: User Fee Waivers, Reductions and Refunds for Drug and Biological Products, OPC claims an exemption from the requirement for an application fee because this sNDA is for an indication that has Orphan Designation. User fee identification number PD3013934 has been assigned to this application.

OPC considers the information contained in this sNDA to be confidential and proprietary. We therefore request that no information contained in this sNDA be disclosed to third parties, through freedom of information (FOI) requests or otherwise, without first obtaining written consent from OPC.

If there are any questions or comments concerning this submission, please contact Mr. Patrick Guinn, Associate Director, Global Regulatory Affairs at 240-683-3277 (e-mail: Patrick.Guinn@otsuka-us.com).

Sincerely,

[See appended electronic signature page]

David Goldberger, RPh, RAC
Vice President, Global Regulatory Affairs
Otsuka Pharmaceutical Development & Commercialization, Inc.

Otsuka Pharmaceutical Development & Commercialization, Inc.
This page is a manifestation of an electronically capture signature

OPC-14597

SIGNATUR PAG

Document Name: 21436_Cover Letter_SN0045_Tourettes sNDA Submission

Document Number: 0001033643

Document Version: 4.0

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)
Goldberger_David	Regulatory Affairs Approval	11-Feb-2014 15:50 GMT+00

Otsuka Pharmaceuticals Development & Commercialization, Inc.

Electronic Submission Information

Approximate size of the submission	1.5 GB
Type and number of electronic media	via Electronic Submission Gateway
This submission is virus-free	Name: **Trend Micro OfficeScan Client for Windows Version 10.6.2108 Service Pack 1**

Technical point of contact:

Boris Reznichenko, MS
Senior Regulatory Submissions Associate, Regulatory Affairs
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Princeton, NJ 08540

Phone: (609) 249-7232
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E-mail: boris.reznichenko@otsuka-us.com

EXHIBIT D

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 21436/S-038
NDA 21713/S-030
NDA 21729/S-022
NDA 21866/S-023

SUPPLEMENT APPROVAL

Otsuka Pharmaceutical Development & Commercialization, Inc.
Attention: David Goldberger, RPh, RAC
Vice President, Global Regulatory Affairs
2440 Research Blvd.
Rockville, MD 20850

Dear Mr. Goldberger:

Please refer to your Supplemental New Drug Applications (sNDA) dated and received February 12, 2014 (NDA 21436/S-038), and April 3, 2014 (NDAs 21713/S-030, 21729/S-022, 21866/S-023), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Abilify (aripiprazole) tablets 2 mg, 5 mg, 10 mg, 15 mg, 20 mg, 30 mg (NDA 21436), oral solution 1 mg/ml (NDA 21713), orally disintegrating tablet 10 mg, 15 mg (NDA 21729), and injectable formulation 9.75 mg/1.3 mL single-dose vial (NDA 21866).

We acknowledge receipt of your amendments dated March 7, 2014; March 26, 2014; April 30, 2014; June 10, 2014; June 20, 2014; June 26, 2014; August 29, 2014; October 28, 2014; November 14, 2014; November 24, 2014; December 2, 2014, December 8, 2014, and December 9, 2014.

These "Prior Approval" supplemental new drug applications provide for labeling revisions based upon two adequate and well-controlled trials that demonstrate the efficacy for the new indication in pediatric patients with Tourette's Disorder.

APPROVAL & LABELING

We have completed our review of these supplemental applications, as amended. They are approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

WAIVER OF HIGHLIGHTS SECTION

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the package insert, Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

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.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment agreed upon in your communication dated November 14, 2014:

2837-1 A controlled trial to evaluate the longer-term (i.e., maintenance) efficacy of aripiprazole in the treatment of pediatric patients (6-17 years) Tourette's

Disorder. This trial must include a placebo group and more than one fixed dose and must utilize a randomized withdrawal design, following an adequate period of stabilization with open-label treatment of aripiprazole. Because it is important to establish the dose-response for maintenance, this trial should randomize patients on stable doses of aripiprazole and different doses of aripiprazole (and to placebo) during the maintenance phase.

The timetable you submitted on November 25, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 01/31/2016
Trial Completion: 07/31/2021
Final Report Submission: 07/31/2022

Submit clinical protocols to your IND 116003 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to this postmarketing commitment should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit the following, in triplicate, (1) a cover letter requesting advisory comments, (2) the proposed materials in draft or mock-up form with annotated references, and (3) the package insert(s) to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

You must submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

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, please call CAPT William Bender, Senior Regulatory Project Manager, at (301) 796-2145 or via email at william.bender@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Mitchell V. Mathis, M.D.
CAPT, USPHS
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:
Content of 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

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS and SUICIDAL THOUGHTS AND BEHAVIORS WITH 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)**
- **Increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants. Monitor for worsening and emergence of suicidal thoughts and behaviors. (5.2)**

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

Indication, Treatment of Tourette's Disorder (1)	12/2014
Dosage and Administration, Tourette's Disorder (2.5)	12/2014
Warnings and Precautions, Metabolic Changes (5.6)	12/2014

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

ABILIFY is an atypical antipsychotic. The oral formulations are indicated for:

- Schizophrenia (14.1)
- Acute Treatment of Manic and Mixed Episodes associated with Bipolar I (14.2)
- Adjunctive Treatment of Major Depressive Disorder (14.3)
- Irritability Associated with Autistic Disorder (14.4)
- Treatment of Tourette's disorder (14.5)

The injection is indicated for:

- Agitation associated with schizophrenia or bipolar mania (14.6)

----------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 (2.2)		15 mg/day	15 mg/day	30 mg/day
Bipolar mania – adults: adjunct to lithium or valproate (2.2)		10-15 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
Major Depressive Disorder – Adults adjunct to antidepressants (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
Tourette's disorder – (2.5)	Patients < 50 kg	2 mg/day	5 mg/day	10 mg/day
	Patients ≥ 50 kg	2 mg/day	10 mg/day	20 mg/day
Agitation associated with schizophrenia or bipolar mania – adults (2.6)		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)
- Known CYP2D6 poor metabolizers: Half of the usual dose (2.7)

----------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----------

- *Cerebrovascular Adverse Reactions in Elderly Patients with Dementia-Related Psychosis:* Increased incidence of cerebrovascular adverse *reactions* (e.g., stroke, transient ischemic attack, including fatalities) (5.2)
- *Neuroleptic Malignant Syndrome:* Manage with immediate discontinuation and close monitoring (5.3)
- *Tardive Dyskinesia:* Discontinue if clinically appropriate (5.4)
- *Metabolic Changes:* Atypical antipsychotic drugs have been associated with metabolic changes that include hyperglycemia/diabetes mellitus, dyslipidemia, and body weight gain (5.5)
  - *Hyperglycemia/Diabetes Mellitus:* Monitor glucose regularly in patients with and at risk for diabetes (5.5)
  - *Dyslipidemia:* Undesirable alterations in lipid levels have been observed in patients treated with atypical antipsychotics (5.5)
  - *Weight Gain:* Weight gain has been observed with atypical antipsychotic use. Monitor weight (5.5)
- *Orthostatic Hypotension:* Monitor heart rate and blood pressure and warn patients with known cardiovascular or cerebrovascular disease, and risk of dehydration or syncope (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
- Pediatric patients (6 to 18 years) with Tourette's disorder: sedation, somnolence, nausea, headache, nasopharyngitis, fatigue, increased appetite
- 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

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

Dosage adjustment due to drug interactions (7.1):

Factors	Dosage Adjustment of Abilify
Known CYP2D6 Poor Metabolizers and strong CYP3A4 inhibitors	Administer a quarter of usual dose
Strong CYP2D6 or CYP3A4 inhibitors	Administer half of usual dose
Strong CYP2D6 and CYP3A4 inhibitors	Administer a quarter of usual dose
Strong CYP3A4 inducers	Double usual dose over 1 to 2 weeks

----------USE IN SPECIFIC POPULATIONS----------

- *Pregnancy:* May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure (8.1)
- *Nursing Mothers:* Discontinue drug or nursing, taking into consideration importance of drug to the mother (8.3)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: December 2014

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS and SUICIDAL THOUGHTS AND BEHAVIORS WITH ANTIDEPRESSANT DRUGS

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 *[see Warnings and Precautions (5.1)]*.

Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term studies. These studies did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in patients over age 24; there was a reduction in risk with antidepressant use in patients aged 65 and older [*see Warnings and Precautions (5.2)*].

In patients of all ages who are started on antidepressant therapy, monitor closely for worsening, and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber [*see Warnings and Precautions (5.2)*].

1 INDICATIONS AND USAGE

ABILIFY Oral Tablets, Orally-Disintegrating Tablets, and Oral Solution are indicated for the treatment of:

- Schizophrenia [*see CLINICAL STUDIES (14.1)]*
- Acute Treatment of Manic and Mixed Episodes associated with Bipolar I Disorder *[see CLINICAL STUDIES (14.2)]*
- Adjunctive Treatment of Major Depressive Disorder *[see CLINICAL STUDIES (14.3)]*
- Irritability Associated with Autistic Disorder *[see CLINICAL STUDIES (14.4)]*
- Treatment of Tourette's Disorder *[see CLINICAL STUDIES (14.5)]*

ABILIFY Injection is indicated for the treatment of:

- Agitation associated with schizophrenia or bipolar mania [*see CLINICAL STUDIES (14.6)]*

2 DOSAGE AND ADMINISTRATION

2.1 Schizophrenia

Adults

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

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)]*. 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

Acute Treatment of Manic and Mixed Episodes

Adults: The recommended starting dose in adults is 15 mg given once daily as monotherapy and 10 mg to 15 mg given once daily as adjunctive therapy with lithium or valproate. ABILIFY can be given without regard to meals. The recommended target dose of ABILIFY is 15 mg/day, as monotherapy or as adjunctive therapy with lithium or valproate. 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.

Pediatrics: The recommended starting dose in pediatric patients (10 to 17 years) as monotherapy is 2 mg/day, with titration to 5 mg/day after 2 days, and a target dose of 10 mg/day after 2 additional days. Recommended dosing as adjunctive therapy to lithium or valproate is the same. Subsequent dose increases, if needed, should be administered in 5 mg/day increments. ABILIFY can be given without regard to meals. *[see CLINICAL STUDIES (14.2)]*.

2.3 Adjunctive Treatment of Major Depressive Disorder

Adults

The recommended starting dose for ABILIFY as adjunctive treatment for patients already taking an antidepressant is 2 mg/day to 5 mg/day. The recommended dosage range is 2 mg/day to 15 mg/day. Dosage adjustments of up to 5 mg/day should occur gradually, at intervals of no less than 1 week *[see CLINICAL STUDIES (14.3)]*. Patients should be periodically reassessed to determine the continued need for maintenance treatment.

2.4 Irritability Associated with Autistic Disorder

Pediatric Patients (6 to 17 years)

The recommended dosage range for the treatment of pediatric patients with irritability associated with autistic disorder is 5 mg/day to 15 mg/day.

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)]*. Patients should be periodically reassessed to determine the continued need for maintenance treatment.

2.5 Tourette's Disorder

Pediatric Patients (6 to 18 years)

The recommended dosage range for Tourette's Disorder is 5 mg/day to 20 mg/day.

For patients weighing less than 50 kg, dosing should be initiated at 2 mg/day with a target dose of 5 mg/day after 2 days. The dose can be increased to 10 mg/day in patients who do not achieve optimal control of tics. Dosage adjustments should occur gradually at intervals of no less than 1 week.

For patients weighing 50 kg or more, dosing should be initiated at 2 mg/day for 2 days, and then increased to 5 mg/day for 5 days, with a target dose of 10 mg/day on day 8. The dose can be increased up to 20 mg/day for patients who do not achieve optimal control of tics. Dosage adjustments should occur gradually in increments of 5 mg/day at intervals of no less than 1 week. *[see CLINICAL STUDIES (14.5)]*.

Patients should be periodically reassessed to determine the continued need for maintenance treatment.

2.6 Agitation Associated with Schizophrenia or Bipolar Mania (Intramuscular Injection)

Adults

The recommended dose in these patients is 9.75 mg. The recommended dosage range is 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 ABILIFY 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. 6)]*.

If ongoing ABILIFY therapy is clinically indicated, oral ABILIFY in a range of 10 mg/day to 30 mg/day should replace ABILIFY 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.

2.7 Dosage Adjustments for Cytochrome P450 Considerations

Dosage adjustments are recommended in patients who are known CYP2D6 poor metabolizers and in patients taking concomitant CYP3A4 inhibitors or CYP2D6 inhibitors or strong CYP3A4 inducers (see Table 1). When the coadministered drug is withdrawn from the combination therapy, ABILIFY dosage should then be adjusted to its original level. When the coadministered CYP3A4 inducer is withdrawn, ABILIFY dosage should be reduced to the original level over 1 to 2 weeks. Patients who may be receiving a combination of strong, moderate, and weak inhibitors of CYP3A4 and CYP2D6 (e.g., a strong CYP3A4 inhibitor and a moderate CYP2D6 inhibitor or a moderate CYP3A4 inhibitor with a moderate CYP2D6 inhibitor), the dosing may be reduced to one-quarter (25%) of the usual dose initially and then adjusted to achieve a favorable clinical response.

Table 1: Dose Adjustments for ABILIFY in Patients who are known CYP2D6 Poor Metabolizers and Patients Taking Concomitant CYP2D6 Inhibitors, 3A4 Inhibitors, and/or CYP3A4 Inducers

Factors	**Dosage Adjustments for ABILIFY**
Known CYP2D6 Poor Metabolizers	Administer half of usual dose
Known CYP2D6 Poor Metabolizers taking concomitant strong CYP3A4 inhibitors (e.g., itraconazole, clarithromycin)	Administer a quarter of usual dose
Strong CYP2D6 (e.g., quinidine, fluoxetine, paroxetine) **or** CYP3A4 inhibitors (e.g., itraconazole, clarithromycin)	Administer half of usual dose
Strong CYP2D6 **and** CYP3A4 inhibitors	Administer a quarter of usual dose
Strong CYP3A4 inducers (e.g., carbamazepine, rifampin)	Double usual dose over 1 to 2 weeks

*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)*.

2.8 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)]*.

2.9 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® (aripiprazole) Tablets are available as described in Table 2.

Table 2: ABILIFY Tablet Presentations

Tablet Strength	Tablet Color/Shape	Tablet Markings
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® (aripiprazole) Orally Disintegrating Tablets are available as described in Table 3.

Table 3: ABILIFY DISCMELT Orally Disintegrating Tablet Presentations

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

ABILIFY® (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® (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

ABILIFY is contraindicated in patients with a history of a hypersensitivity reaction to aripiprazole. Reactions have ranged from pruritus/urticaria to anaphylaxis *[see ADVERSE REACTIONS (6.3)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Increased Mortality 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].*

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

In three, 10-week, placebo-controlled studies of ABILIFY in elderly patients with psychosis associated with Alzheimer's disease (n=938; mean age: 82.4 years; range: 56-99 years), the adverse reactions that were reported at an incidence of ≥3% and ABILIFY incidence at least twice that for placebo were lethargy [placebo 2%, ABILIFY 5%], somnolence (including sedation) [placebo 3%, ABILIFY 8%], and incontinence (primarily, urinary incontinence) [placebo 1%, ABILIFY 5%], excessive salivation [placebo 0%, ABILIFY 4%], and lightheadedness [placebo 1%, ABILIFY 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, assess for the emergence of difficulty swallowing or excessive somnolence, which could predispose to accidental injury or aspiration *[see also BOXED WARNING]*.

5.2 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 (e.g., stroke, transient ischemic attack), including fatalities, in ABILIFY-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 ABILIFY. ABILIFY is not approved for the treatment of patients with dementia-related psychosis *[see also BOXED WARNING]*.

5.3 Suicidal Thoughts and Behaviors in Children, Adolescents, and Young Adults

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
	Increases Compared to Placebo
<18	14 additional cases
18-24	5 additional cases
	Decreases Compared to Placebo
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.

5.4 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 ABILIFY. Rare cases of NMS occurred during ABILIFY 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 (e.g., 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.

5.5 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.

5.6 Metabolic Changes

Atypical antipsychotic drugs have been associated with metabolic changes that include hyperglycemia/diabetes mellitus, dyslipidemia, and body weight gain. While all drugs in the class have been shown to produce some metabolic changes, each drug has its own specific risk profile.

Hyperglycemia/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 reports of hyperglycemia in patients treated with ABILIFY *[see ADVERSE REACTIONS (6.2, 6.3)]*. 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 suggest an increased risk of hyperglycemia-related adverse reactions in patients treated with the atypical antipsychotics. 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 reactions 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 (e.g., 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.

Adults

In an analysis of 13 placebo-controlled monotherapy trials in adults, primarily with schizophrenia or bipolar disorder, the mean change in fasting glucose in ABILIFY-treated patients (+4.4 mg/dL; median exposure 25 days; N=1057) was not significantly different than in placebo-treated patients (+2.5 mg/dL; median exposure 22 days; N=799). Table 5 shows the proportion of ABILIFY-treated patients with normal and borderline fasting glucose at baseline (median exposure 25 days) that had treatment-emergent high fasting glucose measurements compared to placebo-treated patients (median exposure 22 days).

Table 5: Changes in Fasting Glucose From Placebo-Controlled Monotherapy Trials in Adult Patients

	Category Change (at least once) from Baseline	Treatment Arm	n/N	%
Fasting Glucose	Normal to High (<100 mg/dL to ≥126 mg/dL)	ABILIFY	31/822	3.8
		Placebo	22/605	3.6
	Borderline to High (≥100 mg/dL and <126 mg/dL to ≥126 mg/dL)	ABILIFY	31/176	17.6
		Placebo	13/142	9.2

At 24 weeks, the mean change in fasting glucose in ABILIFY-treated patients was not significantly different than in placebo-treated patients [+2.2 mg/dL (n=42) and +9.6 mg/dL (n=28), respectively].

The mean change in fasting glucose in adjunctive ABILIFY-treated patients with major depressive disorder (+0.7 mg/dL; median exposure 42 days; N=241) was not significantly different than in placebo-treated patients (+0.8 mg/dL; median exposure 42 days; N=246). Table 6 shows the proportion of adult patients with changes in fasting glucose levels from two placebo-controlled, adjunctive trials (median exposure 42 days) in patients with major depressive disorder.

Table 6: Changes in Fasting Glucose From Placebo-Controlled Adjunctive Trials in Adult Patients with Major Depressive Disorder

	Category Change (at least once) from Baseline	Treatment Arm	n/N	%
Fasting Glucose	Normal to High (<100 mg/dL to ≥126 mg/dL)	ABILIFY	2/201	1.0
		Placebo	2/204	1.0
	Borderline to High (≥100 mg/dL and <126 mg/dL to ≥126 mg/dL)	ABILIFY	4/34	11.8
		Placebo	3/37	8.1

Pediatric Patients and Adolescents

In an analysis of two placebo-controlled trials in adolescents with schizophrenia (13 to 17 years) and pediatric patients with bipolar disorder (10 to 17 years), the mean change in fasting glucose in ABILIFY-treated patients (+4.8 mg/dL; with a median exposure of 43 days; N=259) was not significantly different than in placebo-treated patients (+1.7 mg/dL; with a median exposure of 42 days; N=123).

In an analysis of two placebo-controlled trials in pediatric and adolescent patients with irritability associated with autistic disorder (6 to 17 years) with median exposure of 56 days, the mean change in fasting glucose in ABILIFY-treated patients (–0.2 mg/dL; N=83) was not significantly different than in placebo-treated patients (–0.6 mg/dL; N=33).

In an analysis of two placebo-controlled trials in pediatric and adolescent patients with Tourette's disorder (6 to 18 years) with median exposure of 57 days, the mean change in fasting glucose in ABILIFY-treated patients (0.79 mg/dL; N=90) was not significantly different than in placebo-treated patients (–1.66 mg/dL; N=58).

Table 7 shows the proportion of patients with changes in fasting glucose levels from the pooled adolescent schizophrenia and pediatric bipolar patients (median exposure of 42-43 days), from two placebo-controlled trials in pediatric patients (6 to 17 years) with irritability associated with autistic disorder (median exposure of 56 days), and from the two placebo-controlled trials in pediatric patients (6 to 18 year) with Tourette's Disorder (median exposure 57 days).

Table 7: Changes in Fasting Glucose From Placebo-Controlled Trials in Pediatric and Adolescent Patients

Category Change (at least once) from Baseline	Indication	Treatment Arm	n/N	%
Fasting Glucose Normal to High (<100 mg/dL to ≥126 mg/dL)	Pooled Schizophrenia and Bipolar Disorder	ABILIFY	2/236	0.8
		Placebo	2/110	1.8
	Irritability Associated with Autistic Disorder	ABILIFY	0/73	0
		Placebo	0/32	0
	Tourette's Disorder	ABILIFY	3/88	3.4
		Placebo	1/58	1.7
Fasting Glucose Borderline to High (≥100 mg/dL and <126 mg/dL to ≥126 mg/dL)	Pooled Schizophrenia and Bipolar Disorder	ABILIFY	1/22	4.5
		Placebo	0/12	0
	Irritability Associated with Autistic Disorder	ABILIFY	0/9	0
		Placebo	0/1	0
	Tourette's Disorder	ABILIFY	0/11	0
		Placebo	0/4	0

At 12 weeks in the pooled adolescent schizophrenia and pediatric bipolar disorder trials, the mean change in fasting glucose in ABILIFY-treated patients was not significantly different than in placebo-treated patients [+2.4 mg/dL (n=81) and +0.1 mg/dL (n=15), respectively].

Dyslipidemia

Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.

There were no significant differences between ABILIFY- and placebo-treated patients in the proportion with changes from normal to clinically significant levels for fasting/nonfasting total cholesterol, fasting triglycerides, fasting LDLs, and fasting/nonfasting HDLs. Analyses of patients with at least 12 or 24 weeks of exposure were limited by small numbers of patients.

Adults

Table 8 shows the proportion of adult patients, primarily from pooled schizophrenia and bipolar disorder monotherapy placebo-controlled trials, with changes in total cholesterol (pooled from 17 trials; median exposure 21 to 25 days), fasting triglycerides (pooled from

eight trials; median exposure 42 days), fasting LDL cholesterol (pooled from eight trials; median exposure 39 to 45 days, except for placebo-treated patients with baseline normal fasting LDL measurements, who had median treatment exposure of 24 days) and HDL cholesterol (pooled from nine trials; median exposure 40 to 42 days).

Table 8: Changes in Blood Lipid Parameters From Placebo-Controlled Monotherapy Trials in Adults

	Treatment Arm	n/N	%
Total Cholesterol Normal to High (<200 mg/dL to ≥240 mg/dL)	ABILIFY	34/1357	2.5
	Placebo	27/973	2.8
Fasting Triglycerides Normal to High (<150 mg/dL to ≥200 mg/dL)	ABILIFY	40/539	7.4
	Placebo	30/431	7.0
Fasting LDL Cholesterol Normal to High (<100 mg/dL to ≥160 mg/dL)	ABILIFY	2/332	0.6
	Placebo	2/268	0.7
HDL Cholesterol Normal to Low (≥40 mg/dL to <40 mg/dL)	ABILIFY	121/1066	11.4
	Placebo	99/794	12.5

In monotherapy trials in adults, the proportion of patients at 12 weeks and 24 weeks with changes from Normal to High in total cholesterol (fasting/nonfasting), fasting triglycerides, and fasting LDL cholesterol were similar between ABILIFY- and placebo-treated patients: at 12 weeks, Total Cholesterol (fasting/nonfasting), 1/71 (1.4%) vs. 3/74 (4.1%); Fasting Triglycerides, 8/62 (12.9%) vs. 5/37 (13.5%); Fasting LDL Cholesterol, 0/34 (0%) vs. 1/25 (4.0%), respectively; and at 24 weeks, Total Cholesterol (fasting/nonfasting), 1/42 (2.4%) vs. 3/37 (8.1%); Fasting Triglycerides, 5/34 (14.7%) vs. 5/20 (25%); Fasting LDL Cholesterol, 0/22 (0%) vs. 1/18 (5.6%), respectively.

Table 9 shows the proportion of patients with changes in total cholesterol (fasting/nonfasting), fasting triglycerides, fasting LDL cholesterol, and HDL cholesterol from two placebo-controlled adjunctive trials in adult patients with major depressive disorder (median exposure 42 days).

Table 9: Changes in Blood Lipid Parameters From Placebo-Controlled Adjunctive Trials in Adult Patients with Major Depressive Disorder

	Treatment Arm	n/N	%
Total Cholesterol Normal to High (<200 mg/dL to ≥240 mg/dL)	ABILIFY	3/139	2.2
	Placebo	7/135	5.2
Fasting Triglycerides Normal to High (<150 mg/dL to ≥200 mg/dL)	ABILIFY	14/145	9.7
	Placebo	6/147	4.1
Fasting LDL Cholesterol Normal to High (<100 mg/dL to ≥160 mg/dL)	ABILIFY	0/54	0
	Placebo	0/73	0
HDL Cholesterol Normal to Low (≥40 mg/dL to <40 mg/dL)	ABILIFY	17/318	5.3
	Placebo	10/286	3.5

Pediatric Patients and Adolescents

Table 10 shows the proportion of adolescents with schizophrenia (13 to 17 years) and pediatric patients with bipolar disorder (10 to 17 years) with changes in total cholesterol and HDL cholesterol (pooled from two placebo-controlled trials; median exposure 42 to 43 days) and fasting triglycerides (pooled from two placebo-controlled trials; median exposure 42 to 44 days).

Table 10: Changes in Blood Lipid Parameters From Placebo-Controlled Monotherapy Trials in Pediatric and Adolescent Patients in Schizophrenia and Bipolar Disorder

	Treatment Arm	n/N	%
Total Cholesterol Normal to High (<170 mg/dL to ≥200 mg/dL)	ABILIFY	3/220	1.4
	Placebo	0/116	0
Fasting Triglycerides Normal to High (<150 mg/dL to ≥200 mg/dL)	ABILIFY	7/187	3.7
	Placebo	4/85	4.7
HDL Cholesterol Normal to Low (≥40 mg/dL to <40 mg/dL)	ABILIFY	27/236	11.4
	Placebo	22/109	20.2

In monotherapy trials of adolescents with schizophrenia and pediatric patients with bipolar disorder, the proportion of patients at 12 weeks and 24 weeks with changes from Normal to High in total cholesterol (fasting/nonfasting), fasting triglycerides, and fasting LDL cholesterol were similar between ABILIFY- and placebo-treated patients: at 12 weeks, Total Cholesterol (fasting/nonfasting), 0/57 (0%) vs. 0/15 (0%); Fasting

Triglycerides, 2/72 (2.8%) vs. 1/14 (7.1%), respectively; and at 24 weeks, Total Cholesterol (fasting/nonfasting), 0/36 (0%) vs. 0/12 (0%); Fasting Triglycerides, 1/47 (2.1%) vs. 1/10 (10.0%), respectively.

Table 11 shows the proportion of patients with changes in total cholesterol (fasting/nonfasting) and fasting triglycerides (median exposure 56 days) and HDL cholesterol (median exposure 55 to 56 days) from two placebo-controlled trials in pediatric patients (6 to 17 years) with irritability associated with autistic disorder.

Table 11: Changes in Blood Lipid Parameters From Placebo-Controlled Trials in Pediatric Patients with Autistic Disorder

	Treatment Arm	n/N	%
Total Cholesterol Normal to High (<170 mg/dL to ≥200 mg/dL)	ABILIFY	1/95	1.1
	Placebo	0/34	0
Fasting Triglycerides Normal to High (<150 mg/dL to ≥200 mg/dL)	ABILIFY	0/75	0
	Placebo	0/30	0
HDL Cholesterol Normal to Low (≥40 mg/dL to <40 mg/dL)	ABILIFY	9/107	8.4
	Placebo	5/49	10.2

Table 12 shows the proportion of patients with changes in total cholesterol (fasting/nonfasting) and fasting triglycerides (median exposure 57 days) and HDL cholesterol (median exposure 57 days) from two placebo-controlled trials in pediatric patients (6 to 18 years) with Tourette's Disorder.

Table 12: Changes in Blood Lipid Parameters From Placebo-Controlled Trials in Pediatric Patients with Tourette's Disorder

	Treatment Arm	n/N	%
Total Cholesterol Normal to High (<170 mg/dL to ≥200 mg/dL)	ABILIFY	1/85	1.2
	Placebo	0/46	0
Fasting Triglycerides Normal to High (<150 mg/dL to ≥200 mg/dL)	ABILIFY	5/94	5.3
	Placebo	2/55	3.6
HDL Cholesterol Normal to Low (≥40 mg/dL to <40 mg/dL)	ABILIFY	4/108	3.7
	Placebo	2/67	3.0

Weight Gain

Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

Adults

In an analysis of 13 placebo-controlled monotherapy trials, primarily from pooled schizophrenia and bipolar disorder, with a median exposure of 21 to 25 days, the mean change in body weight in ABILIFY-treated patients was +0.3 kg (N=1673) compared to –0.1 kg (N=1100) in placebo-controlled patients. At 24 weeks, the mean change from baseline in body weight in ABILIFY-treated patients was –1.5 kg (n=73) compared to –0.2 kg (n=46) in placebo-treated patients.

In the trials adding ABILIFY to antidepressants, patients first received 8 weeks of antidepressant treatment followed by 6 weeks of adjunctive ABILIFY or placebo in addition to their ongoing antidepressant treatment. The mean change in body weight in patients receiving adjunctive ABILIFY was +1.7 kg (N=347) compared to +0.4 kg (N=330) in patients receiving adjunctive placebo.

Table 13 shows the percentage of adult patients with weight gain ≥7% of body weight by indication.

Table 13: Percentage of Patients From Placebo-Controlled Trials in Adult Patients with Weight Gain ≥7% of Body Weight

	Indication	Treatment Arm	N	Patients n (%)
Weight gain ≥7% of body weight	Schizophrenia[a]	ABILIFY	852	69 (8.1)
		Placebo	379	12 (3.2)
	Bipolar Mania[b]	ABILIFY	719	16 (2.2)
		Placebo	598	16 (2.7)
	Major Depressive Disorder (Adjunctive Therapy)[c]	ABILIFY	347	18 (5.2)
		Placebo	330	2 (0.6)

[a] 4-6 weeks duration. [b] 3 weeks duration. [c] 6 weeks duration.

Pediatric Patients and Adolescents

In an analysis of two placebo-controlled trials in adolescents with schizophrenia (13 to 17 years) and pediatric patients with bipolar disorder (10 to 17 years) with median exposure of 42 to 43 days, the mean change in body weight in ABILIFY-treated patients

was +1.6 kg (N=381) compared to +0.3 kg (N=187) in placebo-treated patients. At 24 weeks, the mean change from baseline in body weight in ABILIFY-treated patients was +5.8 kg (n=62) compared to +1.4 kg (n=13) in placebo-treated patients.

In two short-term, placebo-controlled trials in patients (6 to 17 years) with irritability associated with autistic disorder with median exposure of 56 days, the mean change in body weight in ABILIFY-treated patients was +1.6 kg (n=209) compared to +0.4 kg (n=98) in placebo-treated patients.

In two short-term, placebo-controlled trials in patients (6 to 18 years) with Tourette's Disorder with median exposure of 57 days, the mean change in body weight in ABILIFY-treated patients was +1.5 kg (n=105) compared to +0.4 kg (n=66) in placebo-treated patients.

Table 14 shows the percentage of pediatric and adolescent patients with weight gain ≥7% of body weight by indication.

Table 14: Percentage of Patients From Placebo-Controlled Monotherapy Trials in Pediatric and Adolescent Patients with Weight Gain ≥7% of Body Weight

	Indication	Treatment Arm	N	Patients n (%)
Weight gain ≥7% of body weight	Pooled Schizophrenia and Bipolar Mania[a]	ABILIFY	381	20 (5.2)
		Placebo	187	3 (1.6)
	Irritability Associated with Autistic Disorder[b]	ABILIFY	209	55 (26.3)
		Placebo	98	7 (7.1)
	Tourette's Disorder[c]	ABILIFY	105	21 (20.0)
		Placebo	66	5 (7.6)

[a] 4-6 weeks duration. [b] 8 weeks duration. [c] 8-10 weeks duration.

In an open-label trial that enrolled patients from the two placebo-controlled trials of adolescents with schizophrenia (13 to 17 years) and pediatric patients with bipolar disorder (10 to 17 years), 73.2% of patients (238/325) completed 26 weeks of therapy with ABILIFY. After 26 weeks, 32.8% of patients gained ≥7% of their body weight, not adjusted for normal growth. To adjust for normal growth, z-scores were derived (measured in standard deviations [SD]), which normalize for the natural growth of pediatric patients and adolescents by comparisons to age- and gender-matched population standards. A z-score change <0.5 SD is considered not clinically significant. After 26 weeks, the mean change in z-score was 0.09 SD.

In an open-label trial that enrolled patients from two short-term, placebo-controlled trials, patients (6 to 17 years) with irritability associated with autistic disorder, as well as *de novo* patients, 60.3% (199/330) completed one year of therapy with ABILIFY. The mean change in weight z-score was 0.26 SDs for patients receiving >9 months of treatment.

When treating pediatric patients for any indication, weight gain should be monitored and assessed against that expected for normal growth.

5.7 Orthostatic Hypotension

ABILIFY may cause orthostatic hypotension, perhaps due to its α_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 (ABILIFY 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 18 years of age (n=732) on oral ABILIFY included orthostatic hypotension (0.5%, 0%), postural dizziness (0.4%, 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%). *[see ADVERSE REACTIONS (6.1)]*

The incidence of a significant orthostatic change in blood pressure (defined as a decrease in systolic blood pressure ≥20 mmHg accompanied by an increase in heart rate ≥25 when comparing standing to supine values) for ABILIFY was not meaningfully different from placebo (ABILIFY incidence, placebo incidence): in adult oral ABILIFY-treated patients (4%, 2%), in pediatric oral ABILIFY-treated patients aged 6 to 18 years (0.4%, 1%), or in ABILIFY injection-treated patients (3%, 2%).

ABILIFY 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) *[see DRUG INTERACTIONS (7.1)]*.

If parenteral benzodiazepine therapy is deemed necessary in addition to ABILIFY injection treatment, patients should be monitored for excessive sedation and for orthostatic hypotension *[see DRUG INTERACTIONS (7.1]*.

5.8 Leukopenia, Neutropenia, and Agranulocytosis

In clinical trials and/or postmarketing experience, events of leukopenia and 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)/absolute neutrophil count (ANC) and history of drug-induced leukopenia/neutropenia. In patients with a history of a clinically significant low WBC/ANC or drug-induced leukopenia/neutropenia, perform a complete blood count (CBC) frequently during the first few months of therapy. In such patients, consider discontinuation of ABILIFY at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Monitor patients with clinically significant neutropenia for fever or other symptoms or signs of infection and treat promptly if such symptoms or signs occur. Discontinue ABILIFY in patients with severe neutropenia (absolute neutrophil count <1000/mm3) and follow their WBC counts until recovery.

5.9 Seizures/Convulsions

In short-term, placebo-controlled trials, patients with a history of seizures excluded seizures/convulsions occurred in 0.1% (3/2467) of undiagnosed adult patients treated with oral ABILIFY, in 0.1% (1/732) of pediatric patients (6 to 18 years), and in 0.2% (1/501) of adult ABILIFY injection-treated patients.

As with other antipsychotic drugs, ABILIFY should be used cautiously in patients with a history of seizures or with conditions that lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

5.10 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 (ABILIFY 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% (20/732) of pediatric patients (6 to 18 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.

5.11 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 ABILIFY for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, (e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration) *[see ADVERSE REACTIONS (6.3)]*.

5.12 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)]*.

5.13 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. ABILIFY 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)]*.

6 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

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

- Increased Mortality in Elderly Patients with Dementia-Related Psychosis *[see BOXED WARNING and WARNINGS AND PRECAUTIONS (5.1)]*
- Cerebrovascular Adverse Events, Including Stroke *[see WARNINGS AND PRECAUTIONS (5.2)]*
- Suicidal Thoughts and Behaviors in Children, Adolescents, and Young Adults *[see BOXED WARNING and WARNINGS AND PRECAUTIONS (5.3)]*
- Neuroleptic Malignant Syndrome (NMS) *[see WARNINGS AND PRECAUTIONS (5.4)]*
- Tardive Dyskinesia *[see WARNINGS AND PRECAUTIONS (5.5)]*
- Metabolic Changes *[see WARNINGS AND PRECAUTIONS (5.6)]*
- Orthostatic Hypotension *[see WARNINGS AND PRECAUTIONS (5.7)]*
- Leukopenia, Neutropenia, and Agranulocytosis *[see WARNINGS AND PRECAUTIONS (5.8)]*
- Seizures/Convulsions *[see WARNINGS AND PRECAUTIONS (5.9)]*
- Potential for Cognitive and Motor Impairment *[see WARNINGS AND PRECAUTIONS (5.10)]*
- Body Temperature Regulation *[see WARNINGS AND PRECAUTIONS (5.11)]*
- Suicide *[see WARNINGS AND PRECAUTIONS (5.12)]*
- Dysphagia *[see WARNINGS AND PRECAUTIONS (5.13)]*

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

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

ABILIFY 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 ABILIFY and 749 patients with exposure to ABILIFY injection. A total of 3390 patients were treated with oral ABILIFY for at least 180 days and 1933 patients treated with oral ABILIFY had at least 1 year of exposure.

ABILIFY has been evaluated for safety in 1,686 patients (6 to 18 years) who participated in multiple-dose, clinical trials in schizophrenia, bipolar mania, autistic disorder, or Tourette's disorder and who had approximately 1,342 patient-years of exposure to oral ABILIFY. A total of 959 pediatric patients were treated with oral ABILIFY for at least 180 days and 556 pediatric patients treated with oral ABILIFY had at least 1 year of exposure.

The conditions and duration of treatment with ABILIFY (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.

6.1 Clinical Trials 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 ABILIFY was administered in doses ranging from 2 mg/day to 30 mg/day.

Commonly Observed Adverse Reactions

The only commonly observed adverse reaction associated with the use of ABILIFY in patients with schizophrenia (incidence of 5% or greater and ABILIFY incidence at least twice that for placebo) was akathisia (ABILIFY 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 ABILIFY was administered at doses of 15 mg/day or 30 mg/day.

Commonly Observed Adverse Reactions

Commonly observed adverse reactions associated with the use of ABILIFY in patients with bipolar mania (incidence of 5% or greater and ABILIFY incidence at least twice that for placebo) are shown in Table 15.

Table 15: Commonly Observed Adverse Reactions in Short-Term, Placebo-Controlled Trials of Adult Patients with Bipolar Mania Treated with Oral ABILIFY Monotherapy

	Percentage of Patients Reporting Reaction	
	ABILIFY	Placebo
Preferred Term	**(n=917)**	**(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 16 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 ABILIFY (doses ≥2 mg/day) and for which the incidence in patients treated with ABILIFY was greater than the incidence in patients treated with placebo in the combined dataset.

Table 16: Adverse Reactions in Short-Term, Placebo-Controlled Trials in Adult Patients Treated with Oral ABILIFY

	Percentage of Patients Reporting Reaction[a]	
System Organ Class	**ABILIFY**	**Placebo**
Preferred Term	**(n=1843)**	**(n=1166)**
Eye Disorders		
Blurred Vision	3	1
Gastrointestinal Disorders		
Nausea	15	11
Constipation	11	7
Vomiting	11	6
Dyspepsia	9	7
Dry Mouth	5	4
Toothache	4	3

Table 16: Adverse Reactions in Short-Term, Placebo-Controlled Trials in Adult Patients Treated with Oral ABILIFY

	Percentage of Patients Reporting Reaction[a]	
System Organ Class	**ABILIFY**	**Placebo**
Preferred Term	**(n=1843)**	**(n=1166)**
Abdominal Discomfort	3	2
Stomach Discomfort	3	2
General Disorders and Administration Site Conditions		
Fatigue	6	4
Pain	3	2
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal Stiffness	4	3
Pain in Extremity	4	2
Myalgia	2	1
Muscle Spasms	2	1
Nervous System Disorders		
Headache	27	23
Dizziness	10	7
Akathisia	10	4
Sedation	7	4
Extrapyramidal Disorder	5	3
Tremor	5	3
Somnolence	5	3
Psychiatric Disorders		
Agitation	19	17
Insomnia	18	13
Anxiety	17	13
Restlessness	5	3
Respiratory, Thoracic, and Mediastinal Disorders		
Pharyngolaryngeal Pain	3	2
Cough	3	2

[a] Adverse reactions reported by at least 2% of patients treated with oral ABILIFY, 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 ABILIFY 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 ABILIFY compared to 6% for patients treated with adjunctive placebo. The most common adverse drug reactions associated with discontinuation in the adjunctive ABILIFY-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 ABILIFY 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 17 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 ABILIFY (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 17: Adverse Reactions in a Short-Term, Placebo-Controlled Trial of Adjunctive Therapy in Patients with Bipolar Disorder

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

[a] Adverse reactions reported by at least 2% of patients treated with oral ABILIFY, 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 ABILIFY 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 ABILIFY-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 ABILIFY in adolescent patients with schizophrenia (incidence of 5% or greater and ABILIFY 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 ABILIFY 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 ABILIFY-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 ABILIFY in pediatric patients with bipolar mania (incidence of 5% or greater and ABILIFY incidence at least twice that for placebo) are shown in Table 18.

Table 18: Commonly Observed Adverse Reactions in Short-Term, Placebo-Controlled Trials of Pediatric Patients (10 to 17 years) with Bipolar Mania Treated with Oral ABILIFY

	Percentage of Patients Reporting Reaction	
Preferred Term	**ABILIFY (n=197)**	**Placebo (n=97)**
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 ABILIFY 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 ABILIFY-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 ABILIFY in pediatric patients with autistic disorder (incidence of 5% or greater and ABILIFY incidence at least twice that for placebo) are shown in Table 19.

Table 19: Commonly Observed Adverse Reactions in Short-Term, Placebo-Controlled Trials of Pediatric Patients (6 to 17 years) with Autistic Disorder Treated with Oral ABILIFY

	Percentage of Patients Reporting Reaction	
Preferred Term	**ABILIFY (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

Pediatric Patients (6 to 18 years) with Tourette's Disorder

The following findings are based on one 8-week and one 10-week, placebo-controlled trials in which oral ABILIFY was administered in doses of 2 mg/day to 20 mg/day.

Adverse Reactions Associated with Discontinuation of Treatment

The incidence of discontinuation due to adverse reactions between ABILIFY-treated and placebo-treated pediatric patients (6 to 18 years) was 7% and 1%, respectively.

Commonly Observed Adverse Reactions

Commonly observed adverse reactions associated with the use of ABILIFY in pediatric patients with Tourette's disorder (incidence of 5% or greater and ABILIFY incidence at least twice that for placebo) are shown in Table 20.

Table 20: Commonly Observed Adverse Reactions in Short-Term, Placebo-Controlled Trials of Pediatric Patients (6 to 18 years) with Tourette's Disorder Treated with Oral ABILIFY

	Percentage of Patients Reporting Reaction	
Preferred Term	**ABILIFY (n=121)**	**Placebo (n=72)**
Sedation	13	6
Somnolence	13	1
Nausea	11	4
Headache	10	3
Nasopharyngitis	9	0
Fatigue	8	0
Increased Appetite	7	1

Less Common Adverse Reactions in Pediatric Patients (6 to 18 years) with Schizophrenia, Bipolar Mania, Autistic Disorder, or Tourette's Disorder

Table 21 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, up to 8 weeks in autistic disorder, and up to 10 weeks in Tourette's disorder), including only those reactions that occurred in 2% or more of pediatric patients treated with ABILIFY (doses ≥2 mg/day) and for which the incidence in patients treated with ABILIFY was greater than the incidence in patients treated with placebo.

Table 21: Adverse Reactions in Short-Term, Placebo-Controlled Trials of Pediatric Patients (6 to 18 years) Treated with Oral ABILIFY

	Percentage of Patients Reporting Reaction[a]	
System Organ Class	**ABILIFY**	**Placebo**
Preferred Term	**(n=732)**	**(n=370)**
Eye Disorders		
Blurred Vision	3	0
Gastrointestinal Disorders		
Abdominal Discomfort	2	1

Table 21: Adverse Reactions in Short-Term, Placebo-Controlled Trials of Pediatric Patients (6 to 18 years) Treated with Oral ABILIFY

	Percentage of Patients Reporting Reaction[a]	
System Organ Class	**ABILIFY**	**Placebo**
Preferred Term	**(n=732)**	**(n=370)**
Vomiting	8	7
Nausea	8	4
Diarrhea	4	3
Salivary Hypersecretion	4	1
Abdominal Pain Upper	3	2
Constipation	2	2
General Disorders and Administration Site Conditions		
Fatigue	10	2
Pyrexia	4	1
Irritability	2	1
Asthenia	2	1
Infections and Infestations		
Nasopharyngitis	6	3
Investigations		
Weight Increased	3	1
Metabolism and Nutrition Disorders		
Increased Appetite	7	3
Decreased Appetite	5	4
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal Stiffness	2	1
Muscle Rigidity	2	1
Nervous System Disorders		
Somnolence	16	4
Extrapyramidal Disorder	6	1
Headache	12	10
Sedation	9	2
Akathisia	6	4
Tremor	9	1
Drooling	3	0
Dizziness	3	2
Lethargy	3	0
Dystonia	2	1
Respiratory, Thoracic, and Mediastinal Disorders		
Epistaxis	2	1
Skin and Subcutaneous Tissue Disorders		
Rash	2	1

Table 21: Adverse Reactions in Short-Term, Placebo-Controlled Trials of Pediatric Patients (6 to 18 years) Treated with Oral ABILIFY

	Percentage of Patients Reporting Reaction[a]	
System Organ Class	**ABILIFY**	**Placebo**
Preferred Term	**(n=732)**	**(n=370)**

[a] Adverse reactions reported by at least 2% of pediatric patients treated with oral ABILIFY, except adverse reactions which had an incidence equal to or less than placebo.

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 ABILIFY 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 ABILIFY-treated patients and 2% for adjunctive placebo-treated patients.

Commonly Observed Adverse Reactions

The commonly observed adverse reactions associated with the use of adjunctive ABILIFY in patients with major depressive disorder (incidence of 5% or greater and ABILIFY 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 22 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 ABILIFY (doses ≥2 mg/day) and for which the incidence in patients treated with adjunctive ABILIFY was greater than the incidence in patients treated with adjunctive placebo in the combined dataset.

Table 22: Adverse Reactions in Short-Term, Placebo-Controlled Adjunctive Trials in Patients with Major Depressive Disorder

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

[a] Adverse reactions reported by at least 2% of patients treated with adjunctive ABILIFY, 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 ABILIFY injection was administered at doses of 5.25 mg to 15 mg.

Commonly Observed Adverse Reactions

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

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

Table 23 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 ABILIFY injection (doses ≥5.25 mg/day) and for which the incidence in patients treated with ABILIFY injection was greater than the incidence in patients treated with placebo in the combined dataset.

Table 23: Adverse Reactions in Short-Term, Placebo-Controlled Trials in Patients Treated with ABILIFY Injection

	Percentage of Patients Reporting Reaction[a]	
System Organ Class **Preferred Term**	**ABILIFY (n=501)**	**Placebo (n=220)**
Cardiac Disorders		
Tachycardia	2	<1
Gastrointestinal Disorders		
Nausea	9	3
Vomiting	3	1
General Disorders and Administration Site Conditions		
Fatigue	2	1
Nervous System Disorders		
Headache	12	7
Dizziness	8	5
Somnolence	7	4
Sedation	3	2
Akathisia	2	0

[a] Adverse reactions reported by at least 2% of patients treated with ABILIFY 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

ABILIFY 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%).

Tourette's Disorder

In a study of pediatric patients (7 to 17 years of age) with Tourette's disorder, no common adverse reaction(s) had a dose response relationship.

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 ABILIFY-treated patients was 13% vs. 12% for placebo; and the incidence of akathisia-related events for ABILIFY-treated patients was 8% vs. 4% for placebo. In the short-term, placebo-controlled trial of schizophrenia in pediatric patients (13 to 17 years), the incidence of reported EPS-related events, excluding events related to akathisia, for ABILIFY-treated

patients was 25% vs. 7% for placebo; and the incidence of akathisia-related events for ABILIFY-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 ABILIFY and placebo, with the exception of the Barnes Akathisia Scale (ABILIFY, 0.08; placebo, –0.05). In the pediatric (13 to 17 years) schizophrenia trial, the objectively collected data did not show a difference between ABILIFY and placebo, with the exception of the Simpson Angus Rating Scale (ABILIFY, 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 ABILIFY 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 ABILIFY-treated patients was 16% vs. 8% for placebo and the incidence of akathisia-related events for monotherapy ABILIFY-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 ABILIFY-treated patients was 15% vs. 8% for adjunctive placebo and the incidence of akathisia-related events for adjunctive ABILIFY-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 ABILIFY-treated patients was 26% vs. 5% for placebo and the incidence of akathisia-related events for ABILIFY-treated patients was 10% vs. 2% for placebo.

In the adult bipolar mania trials with monotherapy ABILIFY, the Simpson Angus Rating Scale and the Barnes Akathisia Scale showed a significant difference between ABILIFY and placebo (ABILIFY, 0.50; placebo, –0.01 and ABILIFY, 0.21; placebo, –0.05). Changes in the Assessments of Involuntary Movement Scales were similar for the ABILIFY and placebo groups. In the bipolar mania trials with ABILIFY as adjunctive therapy with either lithium or valproate, the Simpson Angus Rating Scale and the Barnes

Akathisia Scale showed a significant difference between adjunctive ABILIFY and adjunctive placebo (ABILIFY, 0.73; placebo, 0.07 and ABILIFY, 0.30; placebo, 0.11). Changes in the Assessments of Involuntary Movement Scales were similar for adjunctive ABILIFY 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 ABILIFY and placebo (ABILIFY, 0.90; placebo, −0.05). Changes in the Barnes Akathisia Scale and the Assessments of Involuntary Movement Scales were similar for the ABILIFY 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 ABILIFY-treated patients was 8% vs. 5% for adjunctive placebo-treated patients; and the incidence of akathisia-related events for adjunctive ABILIFY-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 ABILIFY and adjunctive placebo (ABILIFY, 0.31; placebo, 0.03 and ABILIFY, 0.22; placebo, 0.02). Changes in the Assessments of Involuntary Movement Scales were similar for the adjunctive ABILIFY 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 ABILIFY-treated patients was 18% vs. 2% for placebo and the incidence of akathisia-related events for ABILIFY-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 ABILIFY and placebo (ABILIFY, 0.1; placebo, –0.4). Changes in the Barnes Akathisia Scale and the Assessments of Involuntary Movement Scales were similar for the ABILIFY and placebo groups.

Tourette's Disorder

In the short-term, placebo-controlled trials in Tourette's disorder in pediatric patients (6 to 18 years), the incidence of reported EPS-related events, excluding events related to akathisia, for ABILIFY-treated patients was 7% vs. 6% for placebo and the incidence of akathisia-related events for ABILIFY-treated patients was 4% vs. 6% for placebo.

In the pediatric (6 to 18 years) short-term Tourette's disorder trials, changes in the Simpson Angus Rating Scale, Barnes Akathisia Scale and Assessments of Involuntary Movement Scale were not clinically meaningfully different for ABILIFY and placebo.

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 ABILIFY-treated patients was 2% vs. 2% for placebo and the incidence of akathisia-related events for ABILIFY-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 ABILIFY and placebo.

Dystonia

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.

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 ≤49 days), and were of limited duration (7/12 ≤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 monotherapy study and a long-term adjunctive study with lithium and valproate in bipolar disorder.

Other Adverse Reactions Observed During the Premarketing Evaluation of ABILIFY

The following listing does not include reactions: 1) already listed in previous tables or elsewhere in labeling, 2) for which a drug cause was remote, 3) which were so general as to be uninformative, 4) which were not considered to have significant clinical implications, or 5) which occurred at a rate equal to or less than placebo.

Reactions are categorized by body system according to the following definitions: *frequent* adverse reactions are those occurring in at least 1/100 patients; *infrequent* adverse reactions are those occurring in 1/100 to 1/1000 patients; *rare* reactions are those occurring in fewer than 1/1000 patients:

Adults - Oral Administration

Blood and Lymphatic System Disorders:

rare - thrombocytopenia

Cardiac Disorders:

infrequent – bradycardia, palpitations, *rare* – atrial flutter, cardio-respiratory arrest, atrioventricular block, atrial fibrillation, angina pectoris, myocardial ischemia, myocardial infarction, cardiopulmonary failure

Eye Disorders:

infrequent – photophobia; *rare* - diplopia

Gastrointestinal Disorders:

infrequent - gastroesophageal reflux disease

General Disorders and Administration Site Conditions:

frequent - asthenia; *infrequent* – peripheral edema, chest pain; *rare* – face edema

Hepatobiliary Disorders:

rare - hepatitis, jaundice

Immune System Disorders:

rare- hypersensitivity

Injury, Poisoning, and Procedural Complications:

infrequent– fall; *rare* – heat stroke

Investigations:

frequent - weight decreased, *infrequent* - hepatic enzyme increased, blood glucose increased, blood lactate dehydrogenase increased, gamma glutamyl transferase increased; *rare* – blood prolactin increased, blood urea inceased, blood creatinine

increased, blood bilirubin increased, electrocardiogram QT prolonged, glycosylated hemoglobin increased

Metabolism and Nutrition Disorders:

frequent –anorexia; *infrequent* - *rare* - hypokalemia, hyponatremia, hypoglycemia

Musculoskeletal and Connective Tissue Disorders:

infrequent - muscular weakness, muscle tightness; *rare* – rhabdomyolysis, mobility decreased

Nervous System Disorders:

infrequent - parkinsonism, memory impairment, cogwheel rigidity, hypokinesia, myoclonus, bradykinesia; *rare* – akinesia, myoclonus, coordination abnormal, speech disorder, Grand Mal convulsion; *<1/10,000 patients* - choreoathetosis

Psychiatric Disorders:

infrequent – aggression, loss of libido, delirium; *rare* – libido increased, anorgasmia, tic, homicidal ideation, catatonia, sleep walking

Renal and Urinary Disorders:

rare - urinary retention, nocturia

Reproductive System and Breast Disorders:

infrequent - erectile dysfunction; *rare* – gynaecomastia, menstruation irregular, amenorrhea, breast pain,priapism

Respiratory, Thoracic, and Mediastinal Disorders:

infrequent - nasal congestion, dyspnea

Skin and Subcutaneous Tissue Disorders:

infrequent - rash, hyperhidrosis, pruritus, photosensitivity reaction, alopecia; *rare* - urticaria

Vascular Disorders:

infrequent – hypotension, hypertension;

Pediatric Patients - Oral Administration

Most adverse events observed in the pooled database of 1,686 pediatric patients, aged 6 to 18 years, were also observed in the adult population. Additional adverse reactions observed in the pediatric population are listed below.

Eye Disorders

infrequent - oculogyric crisis

Gastrointestinal Disorders:

infrequent -tongue dry, tongue spasm

Investigations:

frequent - blood insulin increased

Nervous System Disorders:

infrequent - sleep talking

Renal and Urinary Disorders

frequent – enuresis

Skin and Subcutaneous Tissue Disorders:

infrequent - hirsutism

Adults - Intramuscular Injection

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

General Disorders and Administration Site Conditions:

≥1/100 patients - injection site reaction; *≥1/1000 patients and <1/100 patients* - venipuncture site bruise

6.2 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: occurrences of allergic reaction (anaphylactic reaction, angioedema, laryngospasm, pruritus/urticaria, or oropharyngeal spasm), and blood glucose fluctuation.

7 DRUG INTERACTIONS

7.1 Drugs Having Clinically Important Interactions with ABILIFY

Table 24: Clinically Important Drug Interactions with ABILIFY:

Concomitant Drug Name or Drug Class	Clinical Rationale	Clinical Recommendation
Strong CYP3A4 Inhibitors (e.g., itraconazole, clarithromycin) or strong CYP2D6 inhibitors (e.g., quinidine, fluoxetine, paroxetine)	The concomitant use of ABILIFY with strong CYP 3A4 or CYP2D6 inhibitors increased the exposure of aripiprazole compared to the use of ABILIFY alone *[see CLINICAL PHARMACOLOGY (12.3)]*.	With concomitant use of ABILIFY with a strong CYP3A4 inhibitor or CYP2D6 inhibitor, reduce the ABILIFY dosage *[see DOSAGE AND ADMINISTRATION (2.7)]*.
Strong CYP3A4 Inducers (e.g., carbamazepine, rifampin)	The concomitant use of ABILIFY and carbamazepine decreased the exposure of aripiprazole compared to the use of ABILIFY alone *[see CLINICAL PHARMACOLOGY (12.3)]*.	With concomitant use of ABILIFY with a strong CYP3A4 inducer, consider increasing the ABILIFY dosage *[see DOSAGE AND ADMINISTRATION (2.7)]*.
Antihypertensive Drugs	Due to its alpha adrenergic antagonism, aripiprazole has the potential to enhance the effect of certain antihypertensive agents.	Monitor blood pressure and adjust dose accordingly *[see WARNINGS AND PRECAUTIONS (5.7)]*.
Benzodiazepines (e.g., lorazepam)	The intensity of sedation was greater with the combination of oral aripiprazole and lorazepam as compared to that observed with aripiprazole alone. The orthostatic hypotension observed was greater with the combination as compared to that observed with lorazepam alone *[see WARNINGS AND PRECAUTIONS (5.7)]*	Monitor sedation and blood pressure. Adjust dose accordingly.

7.2 Drugs Having No Clinically Important Interactions with ABILIFY

Based on pharmacokinetic studies, no dosage adjustment of ABILIFY is required when administered concomitantly with famotidine, valproate, lithium, lorazepam.

In addition, no dosage adjustment is necessary for substrates of CYP2D6 (e.g., dextromethorphan, fluoxetine, paroxetine, or venlafaxine), CYP2C9 (e.g., warfarin), CYP2C19 (e.g., omeprazole, warfarin, escitalopram), or CYP3A4 (e.g., dextromethorphan) when co-administered with ABILIFY. Additionally, no dosage adjustment is necessary for valproate, lithium, lamotrigine, lorazepam, or sertraline when co-administered with ABILIFY. *[see CLINICAL PHARMACOLOGY (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ABILIFY during pregnancy. For more information contact the National Pregnancy Registry for Atypical Antipsychotics at 1-866-961-2388 or visit http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/.

Risk Summary

Neonates exposed to antipsychotic drugs (including ABILIFY) during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms. Adequate and well controlled studies with ABILIFY have not been conducted in pregnant women. Animal reproduction studies were conducted with aripiprazole in rats and rabbits during organogenesis, and in rats during the pre-and post-natal period. Oral and intravenous aripiprazole administration during organogenesis in rats and/or rabbits at doses higher than the maximum recommended human dose (MRHD) produced fetal death, decreased fetal weight, undescended testicles, delayed skeletal ossification, skeletal abnormalities, and diaphragmatic hernia. Oral and intravenous aripiprazole administration during the pre- and post-natal period in rats at doses higher than the maximum recommended human dose (MRHD) produced prolonged gestation, stillbirths, decreased pup weight, and decreased pup survival. Administer ABILIFY during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Extrapyramidal and/or withdrawal symptoms, including agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder have been reported in neonates who were exposed to antipsychotic drugs (including ABILIFY) during the third trimester of pregnancy. These symptoms have varied in severity. Some neonates recovered within hours or days without specific treatment; others required prolonged hospitalization. Monitor neonates for extrapyramidal and/or withdrawal symptoms.

Data

Animal Data

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

Pregnant rats were treated with oral doses of 3, 10, and 30 mg/kg/day (1, 3, and 10 times the maximum recommended human dose [MRHD] on a mg/m^2 basis) of aripiprazole during the period of organogenesis. Gestation was slightly prolonged at 30 mg/kg/day. Treatment at the high dose of 30mg/kg/day caused a slight delay in fetal development (decreased fetal weight), undescended testes, and delayed skeletal ossification (also seen at 10 mg/kg/day). There were no adverse effects on embryofetal or pup survival. Delivered offspring had decreased body weights (10 and 30 mg/kg/day), and increased incidences of hepatodiaphragmatic nodules and diaphragmatic hernia at 30 mg/kg (the other dose groups were not examined for these findings). Postnatally, delayed vaginal opening was seen at 10 and 30 mg/kg/day 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/day. Some maternal toxicity was seen at 30 mg/kg/day however, there was no evidence to suggest that these developmental effects were secondary to maternal toxicity.

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

Pregnant rabbits were treated with oral doses of 10, 30 , and 100 mg/kg/day (2 , 3, and 11 times human exposure at MRHD based on AUC and 6, 19 , and 65 times the MRHD based on mg/m^2) of aripiprazole during the period of organogenesis. At the high dose of 100mg/kg/day decreased maternal food consumption, and increased abortions were seen as well as increased fetal mortality , decreased fetal weight (also seen at 30 mg/kg/day), increased incidence of a skeletal abnormality (fused sternebrae)(also seen at 30 mg/kg/day).

In pregnant rabbits receiving aripiprazole injection intravenously (3, 10 , 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/day, which is 5 times the human exposure at the MRHD based on AUC and is 6 times the MRHD based on mg/m^2.

In a study in which rats were treated peri- and post-natally with oral doses of 3, 10, and 30 mg/kg/day (1, 3, and 10 times the MRHD on a mg/m^2 basis) of aripiprazole from gestation day 17 through day 21 postpartum, slight maternal toxicity, slightly prolonged gestation an increase in stillbirths and, decreases in pup weight (persisting into adulthood) and survival were seen at 30mg/kg/day.

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

8.3 Nursing Mothers

ABILIFY is present in human breast milk. Because of the potential for serious adverse reactions in nursing infants from ABILIFY, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

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.

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 weight *[see CLINICAL PHARMACOLOGY (12.3)]*.

Schizophrenia

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 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.

Bipolar I Disorder

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 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.

Irritability Associated with Autistic Disorder

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 DOSAGE AND ADMINISTRATION (2.4), ADVERSE REACTIONS (6.2), and CLINICAL STUDIES (14.4)]*. Maintenance efficacy in pediatric patients has not been systematically evaluated.

Tourette's Disorder

Safety and effectiveness of aripiprazole in pediatric patients with Tourette's Disorder were established in one 8 week (aged 7 to 17) and one 10 week trial (aged 6 to 18) in 194 pediatric patients *[see DOSAGE AND ADMINISTRATION (2.5), ADVERSE REACTIONS (6.2), and CLINICAL STUDIES (14.5)]*. Maintenance efficacy in pediatric patients has not been systematically evaluated.

Juvenile Animal Studies

Aripiprazole in juvenile rats caused mortality, CNS clinical signs, impaired memory and learning, and delayed sexual maturation when administered at oral doses of 10, 20, 40mg/kg/day from weaning (21 days old) through maturity (80 days old). At 40mg/kg/day, mortality, decreased activity, splayed hind limbs, hunched posture, ataxia,

tremors and other CNS signs were observed in both genders. In addition, delayed sexual maturation was observed in males. At all doses and in a dose-dependent manner, impaired memory and learning, increased motor activity, and histopathology changes in the pituitary (atrophy), adrenals (adrenocortical hypertrophy), mammary glands (hyperplasia and increased secretion), and female reproductive organs (vaginal mucification, endometrial atrophy, decrease in ovarian corpora lutea) were observed. The changes in female reproductive organs were considered secondary to the increase in prolactin serum levels. A No Observed Adverse Effect Level (NOAEL) could not be determined and, at the lowest tested dose of 10mg/kg/day, there is no safety margin relative to the systemic exposures (AUC0-24) for aripiprazole or its major active metabolite in adolescents at the maximum recommended pediatric dose of 15 mg/day. All drug-related effects were reversible after a 2-month recovery period, and most of the drug effects in juvenile rats were also observed in adult rats from previously conducted studies.

Aripiprazole in juvenile dogs (2 months old) caused CNS clinical signs of tremors, hypoactivity, ataxia, recumbency and limited use of hind limbs when administered orally for 6 months at 3, 10, 30mg/kg/day. Mean body weight and weight gain were decreased up to 18% in females in all drug groups relative to control values. A NOAEL could not be determined and, at the lowest tested dose of 3mg/kg/day, there is no safety margin relative to the systemic exposures (AUC0-24) for aripiprazole or its major active metabolite in adolescents at the maximum recommended pediatric dose of 15 mg/day. All drug-related effects were reversible after a 2-month recovery period.

8.5 Geriatric Use

No dosage adjustment is recommended for elderly patients *[see also BOXED WARNING, WARNINGS AND PRECAUTIONS (5.1), and CLINICAL PHARMACOLOGY (12.3)]*.

Of the 13,543 patients treated with oral ABILIFY in clinical trials, 1073 (8%) were ≥65 years old and 799 (6%) were ≥75 years old. Placebo-controlled studies of oral ABILIFY 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 ABILIFY injection in clinical trials, 99 (13%) were ≥65 years old and 78 (10%) were ≥75 years old. Placebo-controlled studies of ABILIFY

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.

ABILIFY is not approved for the treatment of patients with psychosis associated with Alzheimer's disease *[see also BOXED WARNING and WARNINGS AND PRECAUTIONS (5.1)]*.

8.6 CYP2D6 Poor Metabolizers

Dosage adjustment is recommended in known CYP2D6 poor metabolizers due to high aripiprazole concentrations. Approximately 8% of Caucasians and 3–8% of Black/African Americans cannot metabolize CYP2D6 substrates and are classified as poor metabolizers (PM) [*see DOSAGE AND ADMINISTRATION (2.7) and CLINICAL PHARMACOLOGY (12.3)*].

8.7 Hepatic and Renal Impairment

No dosage adjustment for ABILIFY is required on the basis of a patient's hepatic function (mild to severe hepatic impairment, Child-Pugh score between 5 and 15), or renal function (mild to severe renal impairment, glomerular filtration rate between 15 and 90 mL/minute) *[see CLINICAL PHARMACOLOGY (12.3)]*.

8.8 Other Specific Populations

No dosage adjustment for ABILIFY is required on the basis of a patient's sex, race, or smoking status *[see CLINICAL PHARMACOLOGY (12.3)]*.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

ABILIFY is not a controlled substance.

9.2 Abuse and Dependence

ABILIFY 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 (e.g., 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

In clinical trials and in postmarketing experience, adverse reactions of deliberate or accidental overdosage with oral ABILIFY have been reported worldwide. These include overdoses with oral ABILIFY alone and in combination with other substances. No fatality was reported with ABILIFY alone. The largest known dose with a known outcome involved acute ingestion of 1260 mg of oral ABILIFY (42 times the maximum recommended daily dose) by a patient who fully recovered. Deliberate or accidental overdosage was also reported in children (age 12 and younger) involving oral ABILIFY ingestions up to 195 mg with no fatalities.

Common adverse reactions (reported in at least 5% of all overdose cases) reported with oral ABILIFY overdosage (alone or in combination with other substances) include vomiting, somnolence, and tremor. Other clinically important signs and symptoms observed in one or more patients with ABILIFY 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

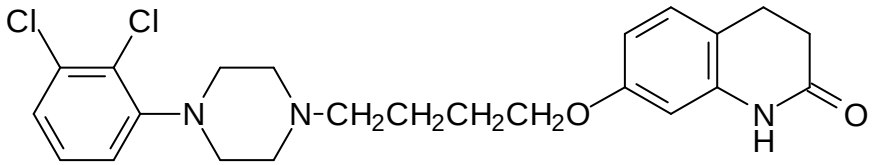
No specific information is available on the treatment of overdose with ABILIFY. An electrocardiogram should be obtained in case of overdosage and if QT interval prolongation is present, cardiac monitoring should be instituted. Otherwise, management of overdose should concentrate on supportive therapy, 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 ABILIFY, decreased the mean AUC and Cmax of aripiprazole by 50%.

Hemodialysis: Although there is no information on the effect of hemodialysis in treating an overdose with ABILIFY, 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® (aripiprazole) Tablets, ABILIFY DISCMELT® (aripiprazole) Orally Disintegrating Tablets, ABILIFY® (aripiprazole) Oral Solution, and ABILIFY® (aripiprazole) Injection, a solution for intramuscular injection. Aripiprazole is 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydrocarbostyril. The empirical formula is $C_{23}H_{27}Cl_2N_3O_2$ and its molecular weight is 448.38. The chemical structure is:



ABILIFY Tablets are available in 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 199.5mg of sulfobutylether β-cyclodextrin (SBECD), 10.4 mg of tartaric acid, qs to pH 4.3 of sodium hydroxide, and qs to 1.33 mL of water for injection.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of aripiprazole in schizophrenia or bipolar mania, is unknown. However, the efficacy of aripiprazole could be 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 (e.g., 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 is dose-proportional. Elimination of aripiprazole is mainly through hepatic metabolism involving two P450 isozymes, CYP2D6 and CYP3A4. For CYP2D6 poor metabolizers, the mean elimination half-life for aripiprazole is about 146 hours.

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 Cmax or AUC of aripiprazole or its active metabolite, dehydro-aripiprazole, but delayed Tmax 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 Cmax 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_2 receptor occupancy indicating brain penetration of aripiprazole in humans.

Metabolism and Elimination

Aripiprazole is metabolized primarily by three biotransformation pathways: dehydrogenation, hydroxylation, and N-dealkylation. Based on *in vitro* studies, CYP3A4 and CYP2D6 enzymes are responsible for dehydrogenation and hydroxylation of aripiprazole, and N-dealkylation is catalyzed by CYP3A4. Aripiprazole is the predominant drug moiety in the systemic circulation. At steady-state, dehydro-aripiprazole, the active metabolite, represents about 40% of aripiprazole AUC in plasma.

Following a single oral dose of [^{14}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.

Drug Interaction Studies

Effects of other drugs on the exposures of aripiprazole and dehydro-aripiprazole are summarized in Figure 1 and Figure 2, respectively. Based on simulation, a 4.5-fold increase in mean Cmax and AUC values at steady-state is expected when extensive metabolizers of CYP2D6 are administered with both strong CYP2D6 and CYP3A4 inhibitors. A 3-fold increase in mean Cmax and AUC values at steady-state is expected in poor metabolizers of CYP2D6 administered with strong CYP3A4 inhibitors.

Figure 1: The effects of other drugs on aripiprazole pharmacokinetics

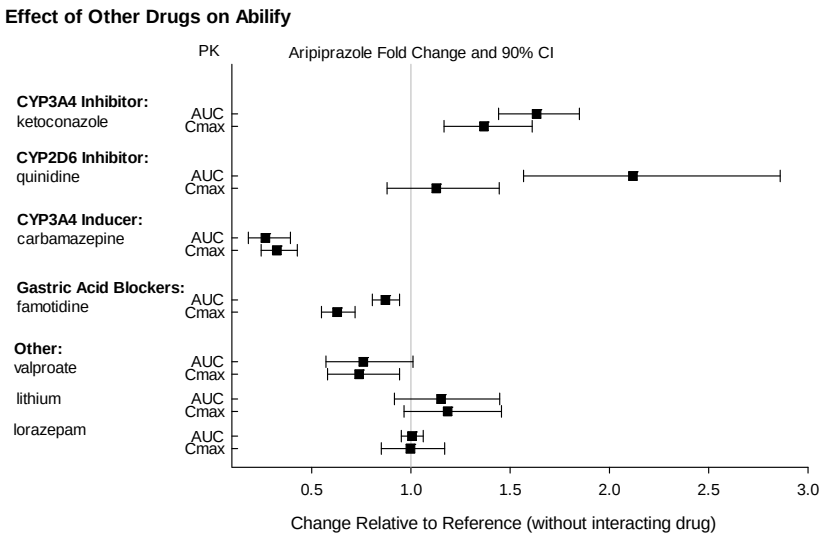
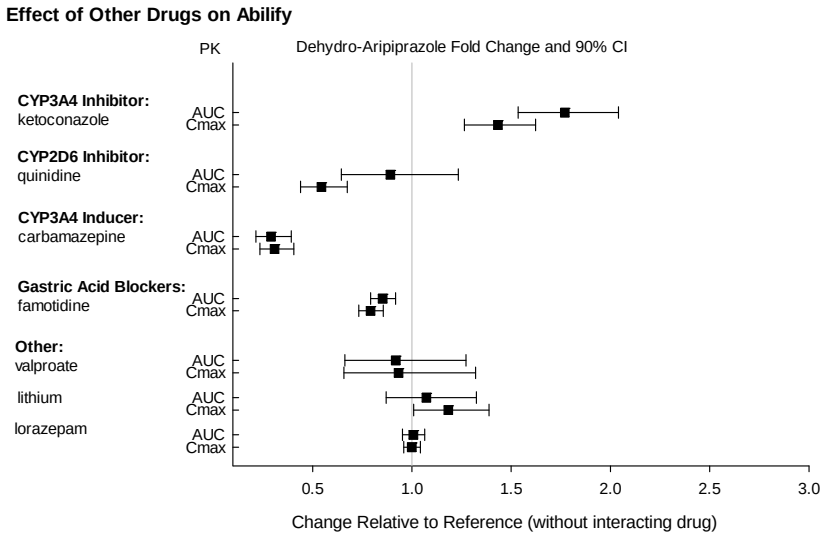
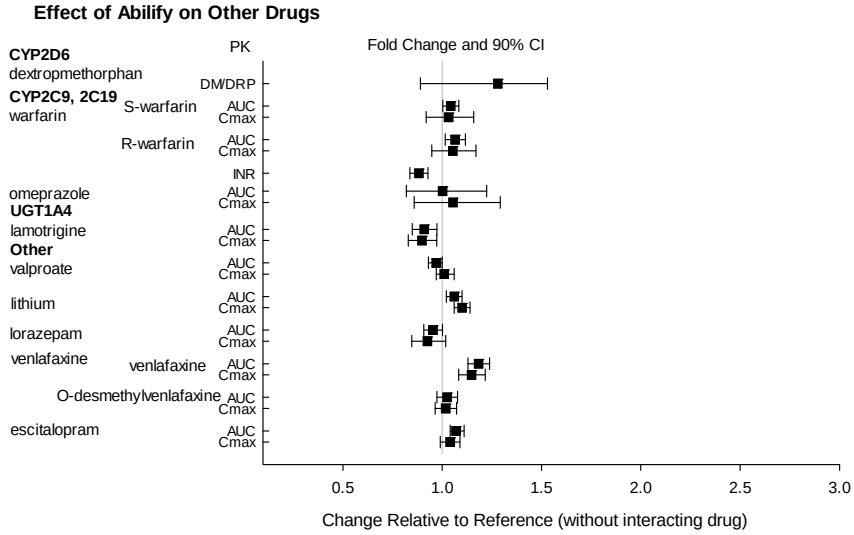


Figure 2: The effects of other drugs on dehydro-aripiprazole pharmacokinetics



The effects of ABILIFY on the exposures of other drugs are summarized in Figure 3. A population PK 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.

Figure 3: The effects of ABILIFY on pharmacokinetics of other drugs



Studies in Specific Populations

Exposures of aripiprazole and dehydro-aripiprazole in specific populations are summarized in Figure 4 and Figure 5, respectively. In addition, in pediatric patients (10 to 17 years of age) administered with Abilify (20 mg to 30 mg), the body weight corrected aripiprazole clearance was similar to the adults.

Figure 4 Effects of intrinsic factors on aripiprazole pharmacokinetics

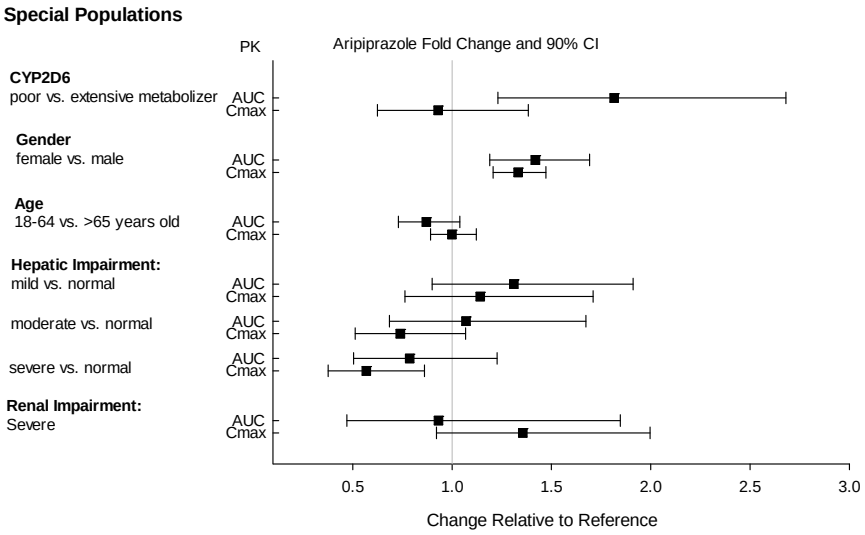
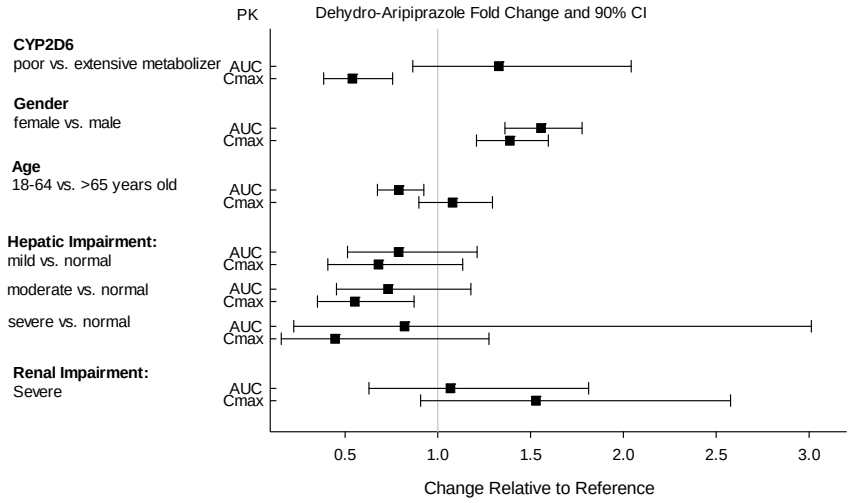


Figure 5: Effects of intrinsic factors on dehydro-aripiprazole pharmacokinetics:



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 Cmax 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, Sprague-Dawley (SD) rats and, F344 rats. Aripiprazole was administered for 2 years in the diet at doses of 1, 3, 10, and 30 mg/kg/day to ICR mice and 1, 3, and 10 mg/kg/day to F344 rats (0.2 to 5 times and 0.3 to 3 times the maximum recommended human dose [MRHD] based on mg/m^2, respectively). In addition, SD rats were dosed orally for 2 years at 10, 20, 40, and 60 mg/kg/day (3 to 19 times the MRHD based on mg/m^2). Aripiprazole did not induce tumors in male mice or male rats. In female mice, the incidences of pituitary gland adenomas and mammary gland adenocarcinomas and adenoacanthomas were increased at dietary doses of 3 to 30 mg/kg/day (0.1 to 0.9 times human exposure at MRHD based on AUC and 0.5 to 5 times the MRHD based on mg/m^2). In female rats, the incidence of mammary gland fibroadenomas was increased at a dietary dose of 10 mg/kg/day (0.1 times human exposure at MRHD based on AUC and 3 times the MRHD based on mg/m^2); and the incidences of adrenocortical carcinomas and combined adrenocortical adenomas/carcinomas were increased at an oral dose of 60 mg/kg/day (14 times human exposure at MRHD based on AUC and 19 times the MRHD based on mg/m^2).

Proliferative changes in the pituitary and mammary gland of rodents have been observed following chronic administration of other antipsychotic agents and are considered prolactin-mediated. Serum prolactin was not measured in the aripiprazole carcinogenicity studies. However, increases in serum prolactin levels were observed in female mice in a 13-week dietary study at the doses associated with mammary gland and pituitary tumors. Serum prolactin was not increased in female rats in 4-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, 6, and 20 mg/kg/day (0.6, 2, and 6 times the maximum recommended human dose [MRHD] on a mg/m^2 basis) of aripiprazole from 2 weeks prior to mating through day 7 of gestation. Estrus cycle irregularities and increased corpora lutea were seen at all doses, but no impairment of fertility was seen. Increased pre-implantation loss was seen at 6 and 20 mg/kg/day and decreased fetal weight was seen at 20 mg/kg/day.

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

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 and 60 mg/kg/day doses are 13 and 19 times the maximum recommended human dose (MRHD) based on mg/m^2 and 7 to 14 times human exposure at MRHD based on AUC. Evaluation of the retinas of albino mice and of monkeys did not reveal evidence of retinal degeneration. Additional studies to further evaluate the

mechanism have not been performed. The relevance of this finding to human risk is unknown.

14 CLINICAL STUDIES

Efficacy of the oral formulations of ABILIFY (aripiprazole) was established in the following adequate and well-controlled trials:

- Four short-term trials and one maintenance trial in adult patients and one short-term trial in adolescents (ages 13-17) with schizophrenia (14.1)
- Four short-term monotherapy trials and one 6-week adjunctive trial in adult patients and one short-term monotherapy trial in pediatric patients (ages 10-17) with manic or mixed episodes (14.2)
- One maintenance monotherapy trial and in one maintenance adjunctive trial in adult patients with bipolar I disorder (14.2)
- Two short-term trials in adult patients with MDD who had an inadequate response to antidepressant therapy during the current episode (14.3)
- Two short-term trials in pediatric patients (ages 6-17 years) for the treatment of irritability associated with autistic disorder (14.4)
- Two short-term trials in pediatric patients (ages 6-18 years) with Tourette's disorder (14.5)

Efficacy of the injectable formulation of ABILIFY (aripiprazole) was established in the following adequate and well-controlled trials:

- Three 24-hour trials in agitated adult patients with schizophrenia or manic/mixed episodes of bipolar I disorder (14.6)

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 ABILIFY 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. Efficacy was evaluated using the total score on the Positive and Negative Syndrome Scale (PANSS).The PANSS is a 30 item scale that measures positive symptoms of schizophrenia (7 items), negative symptoms of schizophrenia (7 items), and general psychopathology (16 items), each rated on a scale of 1 (absent) to 7 (extreme); total PANSS scores range from 30 to 210. 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 (Study 1 in Table 26), 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 (Study 2 in Table 26), 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 (Study 3 in Table 26), 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 (Study 4 in Table 26), 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.

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 ≥5 (minimally worse), scores ≥5 (moderately severe) on the hostility or uncooperativeness items of the PANSS, or ≥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 (Study 5 in Figure 6).

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 ≥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 (Study 6 in Table 26), 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.

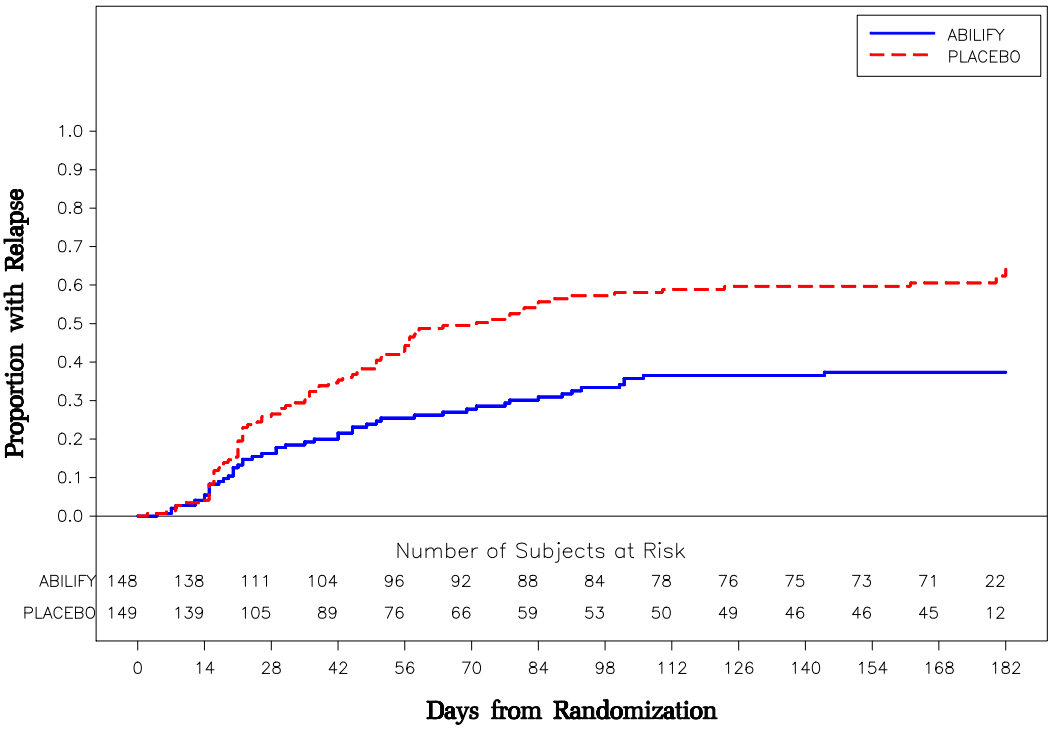
Table 26: Schizophrenia Studies

Study Number	Treatment Group	Primary Efficacy Measure: PANSS		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
Study 1	ABILIFY (15 mg/day)*	98.5 (17.2)	-15.5 (2.40)	-12.6 (-18.9, -6.2)
	ABILIFY (30 mg/day)*	99.0 (19.2)	-11.4 (2.39)	-8.5 (-14.8, -2.1)
	Placebo	100.2 (16.5)	-2.9 (2.36)	--
Study 2	ABILIFY (20 mg/day)*	92.6 (19.5)	-14.5 (2.23)	-9.6 (-15.4, -3.8)
	ABILIFY (30 mg/day)*	94.2 (18.5)	-13.9 (2.24)	-9.0 (-14.8, -3.1)
	Placebo	94.3 (18.5)	-5.0 (2.17)	--
Study 3	ABILIFY (10 mg/day)*	92.7 (19.5)	-15.0 (2.38)	-12.7 (-19.00, -6.41)
	ABILIFY (15 mg/day)*	93.2 (21.6)	-11.7 (2.38)	-9.4 (-15.71, -3.08)
	ABILIFY (20 mg/day)*	92.5 (20.9)	-14.4 (2.45)	-12.1 (-18.53, -5.68)
	Placebo	92.3 (21.8)	-2.3 (2.35)	--
Study 4	ABILIFY (2 mg/day)	90.7 (14.5)	-8.2 (1.90)	-2.9 (-8.29, 2.47)
	ABILIFY (5 mg/day)	92.0 (12.6)	-10.6 (1.93)	-5.2 (-10.7, 0.19)

	ABILIFY (10 mg/day)*	90.0 (11.9)	-11.3 (1.88)	-5.9 (-11.3, -0.58)
	Placebo	90.8 (13.3)	-5.3 (1.97)	--
Study 6 (Pediatric, 13-17 years)	ABILIFY (10 mg/day)*	93.6 (15.7)	-26.7 (1.91)	-5.5 (-10.7, -0.21)
	ABILIFY (30 mg/day)*	94.0 (16.1)	-28.6 (1.92)	-7.4 (-12.7, -2.13)
	Placebo	94.6 (15.6)	-21.2 (1.93)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval.
[a] Difference (drug minus placebo) in least-squares mean change from baseline.
* Doses statistically significantly superior to placebo.

Figure 6: Kaplan-Meier Estimation of Cumulative Proportion of Patients with Relapse (Schizophrenia Study 5)



14.2 Bipolar Disorder

Acute Treatment of Manic and Mixed Episodes

Adults

Monotherapy

The efficacy of ABILIFY as monotherapy 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 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 30 mg/day in two studies and 15 mg/day in two studies), ABILIFY was superior to placebo in the reduction of Y-MRS total score (Studies 1-4 in Table 27) 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.

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 ≥16 and ≤25% improvement on the Y-MRS total score) to lithium or valproate

were randomized to receive either ABILIFY (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 (Study 5 in Table 27) 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.

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 4-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 ≥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 (Study 6 in Table 27).

Table 27: Bipolar Studies

Study Number	Treatment Group	Primary Efficacy Measure: Y-MRS		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
Study 1	ABILIFY (30 / 15 mg/day)*	29.0 (5.9)	-12.52 (1.05)	-5.33 (-7.90, -2.76)
	Placebo	28.5 (4.6)	-7.19 (1.07)	--
Study 2	ABILIFY (30 / 15 mg/day)*	27.8 (5.7)	-8.15 (1.23)	-4.80 (-7.80, -1.80)
	Placebo	29.1 (6.9)	-3.35(1.22)	--
Study 3	ABILIFY (15 - 30 mg/day)*	28.5 (5.6)	-12.64 (0.84)	-3.63 (-5.75 , -1.51)
	Placebo	28.9 (5.9)	9.01 (0.81)	--
Study 4	ABILIFY (15 -30 mg/day)*	28.0 (5.8)	-11.98 (0.80)	-2.28 (-4.44 , -0.11)
	Placebo	28.3 (5.8)	-9.70 (0.83)	--
Study 5	ABILIFY (15 or 30 mg/day)* + Lithium/Valproate	23.2 (5.7)	-13.31 (0.50)	-2.62 (-4.29 , -0.95)
	Placebo + Lithium/Valproate	23.0 (4.9)	-10.70 (0.69)	--
Study 6 (Pediatric, 10-17 years)	ABILIFY (10 mg/day)*	29.8 (6.5)	-14.2 (0.89)	-5.99 (-8.49, -3.50)
	ABILIFY (30 mg/day)*	29.5 (6.3)	-16.5 (0.87)	-8.26 (-10.7, -5.77)
	Placebo	30.7 (6.8)	-8.2 (0.91)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval.
[a] Difference (drug minus placebo) in least-squares mean change from baseline.
* Doses statistically significantly superior to placebo.

Maintenance Treatment of Bipolar I Disorder

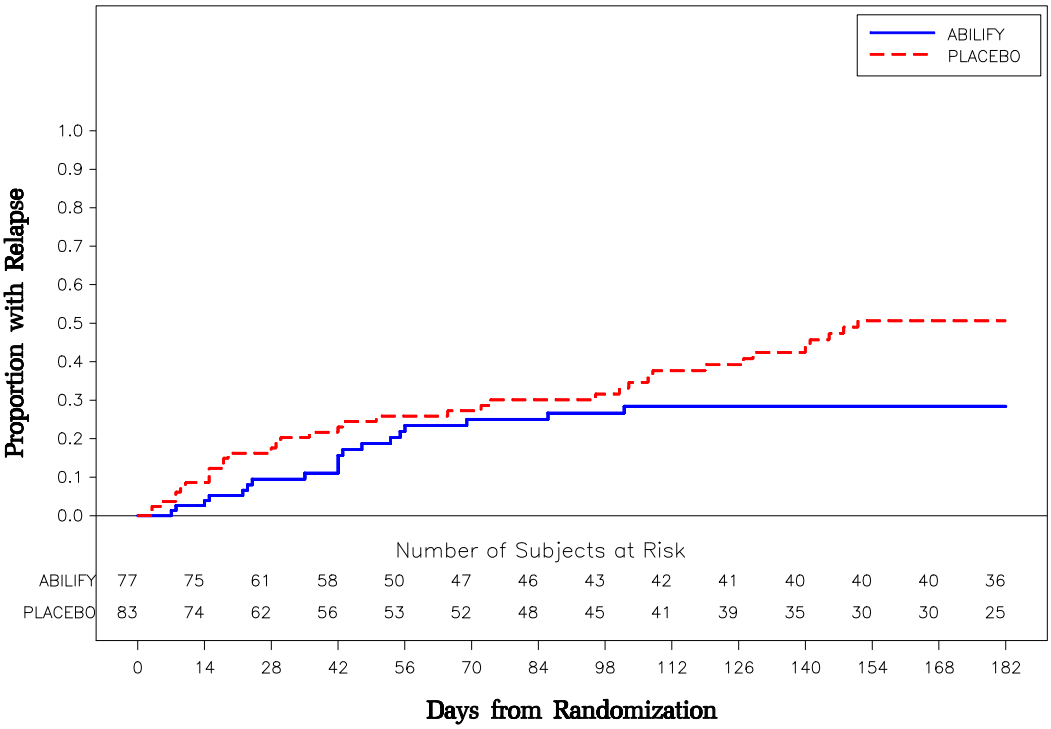
Monotherapy Maintenance Therapy

A maintenance trial was conducted in adult 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 (Study 7 in Figure 7). A total of 55 mood events were observed during the double-blind treatment phase. Nineteen were from the ABILIFY group and 36 were from the placebo group. The number of observed manic episodes in the ABILIFY

group (6) were fewer than that in the placebo group (19), while the number of depressive episodes in the ABILIFY group (9) was similar to that in the placebo group (11).

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.

Figure 7: Kaplan-Meier Estimation of Cumulative Proportion of Patients with Relapse (Bipolar Study 7)

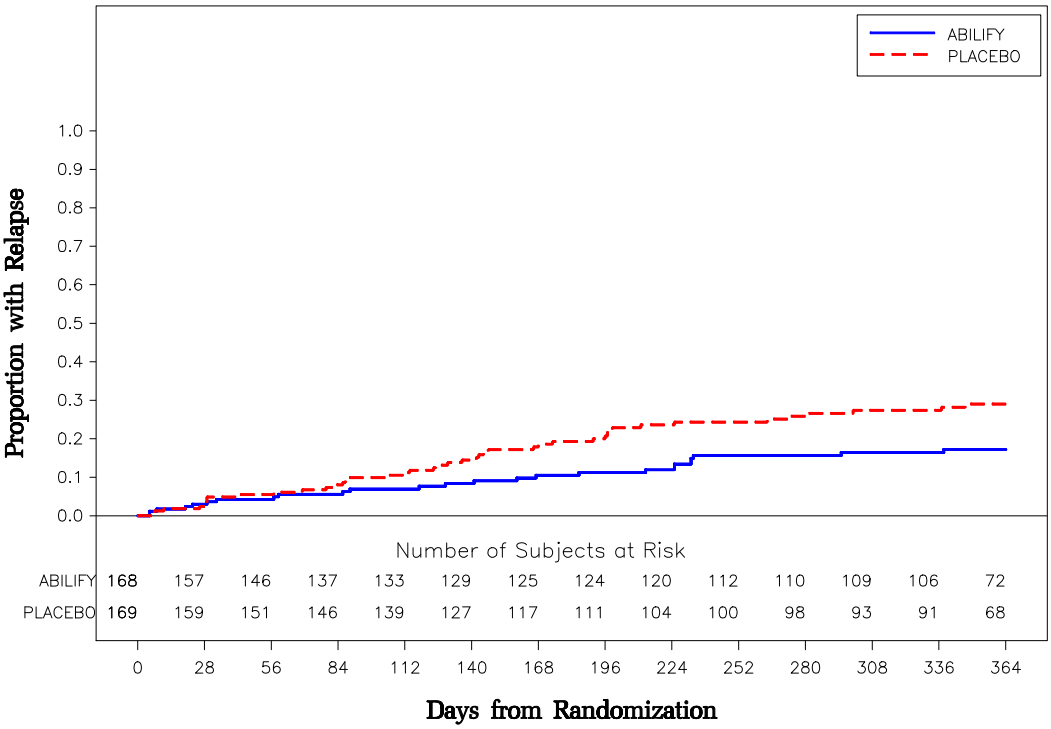


Adjunctive Maintenance Therapy

An adjunctive maintenance trial was conducted in adult patients meeting DSM-IV criteria for bipolar I disorder with a recent manic or mixed episode. 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 ≥16 and ≤35% improvement on the Y-MRS total score) to lithium or valproate received ABILIFY with a starting dose of 15 mg/day with the option to increase to 30 mg or reduce to 10 mg as early as day 4, as adjunctive therapy with open-label lithium or valproate. Prior to

randomization, patients on the combination of single-blind ABILIFY and lithium or valproate were required to maintain stability (Y-MRS and MADRS total scores ≤12) for 12 consecutive weeks. Three hundred thirty-seven patients were then randomized in a double-blind fashion, to either the same dose of ABILIFY they were on at the end of the stabilization period or placebo plus lithium or valproate and were then monitored for manic, mixed, or depressive relapse for a maximum of 52 weeks. ABILIFY was superior to placebo on the primary endpoint, time from randomization to relapse to any mood event (Study 8 in Figure 8). A mood event was defined as hospitalization for a manic, mixed, or depressive episode, study discontinuation due to lack of efficacy accompanied by Y-MRS score >16 and/or a MADRS >16, or an SAE of worsening disease accompanied by Y-MRS score >16 and/or a MADRS >16. A total of 68 mood events were observed during the double-blind treatment phase. Twenty-five were from the ABILIFY group and 43 were from the placebo group. The number of observed manic episodes in the ABILIFY group (7) were fewer than that in the placebo group (19), while the number of depressive episodes in the ABILIFY group (14) was similar to that in the placebo group (18). The Kaplan-Meier curves of the time from randomization to relapse to any mood event during the 52-week, double-blind treatment phase for ABILIFY and placebo groups are shown in Figure 8.

Figure 8: Kaplan-Meier Estimation of Cumulative Proportion of Patients with Relapse to Any Mood Event (Bipolar Study 8)



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.

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 (HAMD17), minimal HAMD17 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. 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 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 (Studies 1, 2 in Table 28). 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.

Table 28: Adjunctive Treatment of Major Depressive Disorder Studies

Study Number	Treatment Group	Primary Efficacy Measure: MADRS		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
Study 1	ABILIFY (5-20 mg/day)* + Antidepressant	25.2(6.2)	-8.49 (0.66)	-2.84 (-4.53 , -1.15)
	Placebo + Antidepressant	27.0 (5.5)	-5.65 (0.64)	--
Study 2	ABILIFY (5-20 mg/day)* + Antidepressant	26.0 (6.0)	-8.78 (0.63)	-3.01 (-4.66 , -1.37)
	Placebo + Antidepressant	26.0 (6.5)	-5.77 (0.67)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval.
[a] Difference (drug minus placebo) in least-squares mean change from baseline.
* Doses statistically significantly superior to placebo.

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 symptoms of irritability in autistic disorder.

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 (Study 1 in Table 29).

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 (Study 2 in Table 29). All three doses of ABILIFY significantly improved scores on the ABC-I subscale compared with placebo.

Table 29: Irritability Associated with Autistic Disorder Studies (Pediatric)

Study Number	Treatment Group	Primary Efficacy Measure: ABC-I		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
Study 1	ABILIFY (2-15 mg/day)*	29.6 (6.37)	-12.9 (1.44)	-7.9 (-11.7, -4.1)
	Placebo	30.2 (6.52)	-5.0 (1.43)	--
Study 2	ABILIFY (5 mg/day)*	28.6 (7.56)	-12.4 (1.36)	-4.0 (-7.7, -0.4)
	ABILIFY (10 mg/day)*	28.2 (7.36)	-13.2 (1.25)	-4.8 (-8.4, -1.3)
	ABILIFY (15 mg/day)*	28.9 (6.41)	-14.4 (1.31)	-6.0 (-9.6, -2.3)
	Placebo	28.0 (6.89)	-8.4 (1.39)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval.
[a] Difference (drug minus placebo) in least-squares mean change from baseline.
* Doses statistically significantly superior to placebo.

14.5 Tourette's Disorder

Pediatric Patients

The efficacy of ABILIFY (aripiprazole) in the treatment of Tourette's disorder was established in one 8-week (7 to 17 years of age) and one 10-week (6 to 18 years of age), placebo-controlled trials in pediatric patients (6 to 18 years of age) who met the DSM-IV criteria for Tourette's disorder and had a Total Tic score (TTS) ≥ 20 - 22 on the Yale Global Tic Severity Scale (YGTSS). The YGTSS is a fully validated scale designed to measure current tic severity. Efficacy was evaluated using two assessment scales: 1) the Total Tic score (TTS) of the YGTSS and 2) the Clinical Global Impressions Scale for Tourette's Syndrome (CGI-TS), a clinician-determined summary measure that takes into account all available patient information. Over 65% of these patients were under 13 years of age.

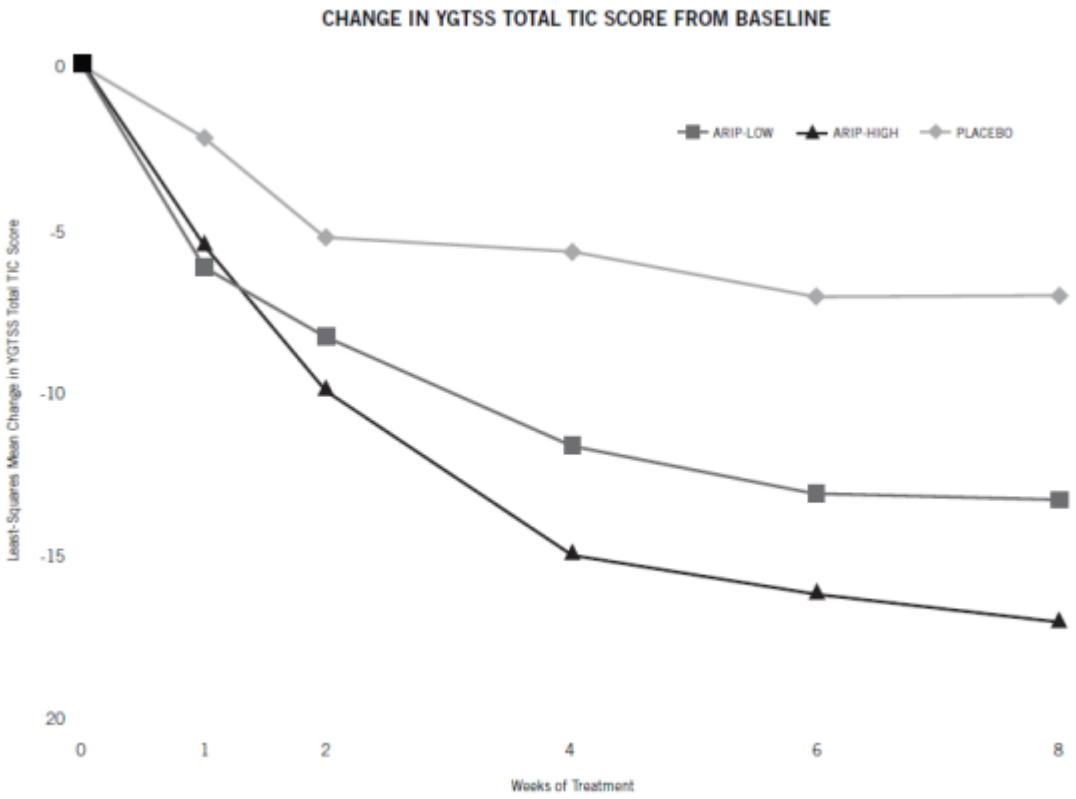
The primary outcome measure in both trials was the change from baseline to endpoint in the TTS of the YGTSS. Ratings for the TTS are made along 5 different dimensions on a scale of 0 to 5 for motor and vocal tics each. Summation of these 10 scores provides a TTS (i.e., 0-50).

The results of these trials are as follows:

In the 8-week, placebo-controlled, fixed-dose trial, children and adolescents with Tourette's disorder (n=133), aged 7 to 17 years, were randomized 1:1:1 to low dose ABILIFY, high dose ABILIFY, or placebo. The target doses for the low and high dose ABILIFY groups were based on weight. Patients < 50 kg in the low dose ABILIFY group started at 2 mg per day with a target dose of 5 mg per day

after 2 days. Patients ≥ 50 kg in the low dose ABILIFY group, started at 2 mg per day increased to 5 mg per day after 2 days, with a subsequent increase to a target dose of 10 mg per day at day 7. Patients <50 kg in the high dose ABILIFY group started at 2 mg per day increased to 5 mg per day after 2 days, with a subsequent increase to a target dose of 10 mg per day at day 7. Patients ≥ 50 kg in the high dose ABILIFY group, started at 2 mg per day increased to 5 mg per day after 2 days, with a subsequent increase to a dose of 10 mg per day at day 7 and were allowed weekly increases of 5 mg per day up to a target dose 20 mg per day at Day 21. ABILIFY (both high and low dose groups) demonstrated statistically significantly improved scores on the YGTSS TTS (Study 1 in Table 30) and on the CGI-TS scale compared with placebo. The estimated improvements on the YGTSS TTS over the course of the study are displayed in Figure 9.

Figure 9: Least Square Means of Change from Baseline in YGTSS TTS by Week (Tourette's Disorder Study 1)



In the 10-week, placebo-controlled, flexible-dose trial in children and adolescents with Tourette's disorder (n=61), aged 6 to 18 years, patients received daily doses of placebo or ABILIFY, starting at 2 mg/day with increases allowed up to 20 mg/day based on clinical response. ABILIFY demonstrated statistically significantly improved scores on the YGTSS TTS scale compared with placebo (Study 2 in Table 30). The mean daily dose of ABILIFY at the end of 10-week treatment was 6.54 mg/day.

Table 30: Tourette's Disorder Studies (Pediatric)

Study Number	Treatment Group	Primary Efficacy Measure: YGTSS TTS		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
Study 1	ABILIFY (low dose)*	29.2 (5.63)	-13.4 (1.59)	-6.3 (-10.2, -2.3)
	ABILIFY (high dose)*	31.2 (6.40)	-16.9 (1.61)	-9.9 (-13.8, -5.9)
	Placebo	30.7 (5.95)	-7.1 (1.55)	--
Study 2	ABILIFY (2-20 mg/day)*	28.3 (5.51)	-15.0 (1.51)	-5.3 (-9.8, -0.9)
	Placebo	29.5 (5.60)	-9.6 (1.64)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval.
[a] Difference (drug minus placebo) in least-squares mean change from baseline.
* Doses statistically significantly superior to placebo.

14.6 Agitation Associated with Schizophrenia or Bipolar Mania

The efficacy of intramuscular ABILIFY 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 ≥15 on the five items comprising the Positive and Negative Syndrome Scale (PANSS) Excited Component (i.e., poor impulse control, tension, hostility, uncooperativeness, and excitement items) with at least two individual item scores ≥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 ABILIFY 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 (Study 1 in Table 31) 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 ABILIFY injection dose of 9.75 mg was evaluated. At 2 hours post-injection, ABILIFY for injection was statistically superior to placebo in the PANSS Excited Component (Study 2 in Table 31) 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 ABILIFY 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 (Study 3 in Table 31).

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

Table 31: Agitation Associated with Schizophrenia or Bipolar Mania Studies

Study Number	Treatment Group	Primary Efficacy Measure: PANSS Excited Component		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
Agitation Associated with Schizophrenia				
Study 1	ABILIFY (1 mg)	19.16 (3.26)	-4.47 (0.72)	-1.19 (-2.96 , 0.59)
	ABILIFY (5.25 mg)*	19.41 (3.31)	-5.65 (0.68)	-2.37 (-4.10 , -0.63)
	ABILIFY (9.75 mg)*	19.42 (2.80)	-6.69 (0.72)	-3.40 (-5.18 , -1.62)
	ABILIFY (15 mg)*	19.34 (2.38)	-5.72 (0.72)	-2.44 (-4.21 , -0.68)
	Placebo	19.18 (2.95)	-3.28 (0.70)	--
Study 2	ABILIFY (9.75 mg)*	18.82 (2.67)	-7.27 (0.59)	-2.48 (-3.77, -1.19)
	Placebo	18.74 (2.71)	-4.78 (0.69)	--
Agitation Associated with Bipolar Mania				
Study 3	ABILIFY (9.75 mg)*	18.77 (2.45)	-8.74 (0.57)	-2.99 (-4.53, -1.44)
	ABILIFY (15 mg)*	18.29 (2.49)	-8.67 (0.57)	-2.91 (-4.44, -1.38)
	Placebo	17.95 (2.63)	-5.76 (0.58)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval.
[a] Difference (drug minus placebo) in least-squares mean change from baseline.
* Doses statistically significantly superior to placebo.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

ABILIFY® (aripiprazole) Tablets have markings on one side and are available in the strengths and packages listed in Table 22.

Table 22: ABILIFY Tablet Presentations

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

Table 22: ABILIFY Tablet Presentations

Tablet Strength	Tablet Color/Shape	Tablet Markings	Pack Size	NDC Code
30 mg	pink round	"A-011" and "30"	Bottle of 30	59148-011-13
			Blister of 100	59148-011-35

ABILIFY DISCMELT® (aripiprazole) Orally Disintegrating Tablets are round tablets with markings on either side. ABILIFY DISCMELT is available in the strengths and packages listed in Table 23.

Table 23: ABILIFY DISCMELT Orally Disintegrating Tablet Presentations

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

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

150 mL bottle NDC 59148-013-15

ABILIFY® (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 25ºC (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

Discuss the following issues with patients prescribed ABILIFY:

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 including information 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 ABILIFY 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 ABILIFY therapy does not affect them adversely *[see WARNINGS AND PRECAUTIONS (5.9)]*.

Nursing

Advise patients that breastfeeding is not recommended with ABILIFY treatment because of the potential for serious adverse reactions in a nursing infant *[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)]*.

Heat Exposure and Dehydration

Patients should be advised regarding appropriate care in avoiding overheating and dehydration *[see WARNINGS AND PRECAUTIONS (5.10)]*.

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

ABILIFY is a trademark of Otsuka Pharmaceutical Company.

03US14L-1121 Rev December 2014

MEDICATION GUIDE

ABILIFY® (a BIL ĭ fī)
(aripiprazole)
Tablets

ABILIFY® (a BIL ĭ fī)
(aripiprazole)
Orally Disintegrating Tablets

ABILIFY® (a BIL ĭ fī)
(aripiprazole)
Oral Solution

ABILIFY® (a BIL ĭ fī)
(aripiprazole)
Injection, for intramuscular use

Read this Medication Guide before you start taking ABILIFY and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is the most important information I should know about ABILIFY?

(For other side effects, also see "**What are the possible side effects of ABILIFY?**").

Serious side effects may happen when you take ABILIFY, including:

- **Increased risk of death in elderly patients with dementia-related psychosis:** Medicines like ABILIFY can raise the risk of death in elderly people who have lost touch with reality (psychosis) due to confusion and memory loss (dementia). ABILIFY is not approved for the treatment of patients with dementia-related psychosis.
- **Risk of suicidal thoughts or actions:** 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.

What is ABILIFY?

- **ABILIFY Oral Tablets, Orally-Disintegrating Tablets, and Oral Solution** are prescription medicines used to treat:
  - Schizophrenia
  - manic or mixed episodes that happen with bipolar I disorder
  - major depressive disorder (MDD) when ABILIFY is used with antidepressant medicines
  - irritability associated with autistic disorder
  - Tourette's disorder
- **ABILIFY Injection** is a prescription medicine used to treat:
  - agitation associated with schizophrenia or bipolar mania

It is not known if ABILIFY is safe or effective in children:

- under 13 years of age with schizophrenia
- under 10 years of age with bipolar I disorder
- under 6 years of age with irritability associated with autistic disorder
- under 6 years of age with Tourette's disorder

Who should not take ABILIFY?

Do not take ABILIFY if you are allergic to aripiprazole or any of the ingredients in ABILIFY. See the end of this Medication Guide for a complete list of ingredients in ABILIFY.

What should I tell my healthcare provider before taking ABILIFY?

Before taking ABILIFY, tell your healthcare provider if you have or had:

- diabetes or high blood sugar in you or your family; your healthcare provider should check your blood sugar before you start ABILIFY and also during therapy.
- seizures (convulsions).
- low or high blood pressure.
- heart problems or stroke.
- pregnancy or plans to become pregnant. It is not known if ABILIFY will harm your unborn baby.
- breast-feeding or plans to breast-feed. ABILIFY can pass into your breast milk and may harm your baby. Talk to your healthcare provider about the best way to feed your baby if you receive ABILIFY.
- low white blood cell count.
- phenylketonuria. ABILIFY DISCMELT Orally Disintegrating Tablets contain phenylalanine.
- any other medical conditions.

Tell your healthcare provider about all the medicines that you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

ABILIFY and other medicines may affect each other causing possible serious side effects. ABILIFY may affect the way other medicines work, and other medicines may affect how ABILIFY works.

Your healthcare provider can tell you if it is safe to take ABILIFY with your other medicines. Do not start or stop any medicines while taking ABILIFY without talking to your healthcare provider first. Know the medicines you take. Keep a list of your medicines to show your healthcare provider and pharmacist when you get a new medicine.

How should I take ABILIFY?

- Take ABILIFY exactly as your healthcare provider tells you to take it. Do not change the dose or stop taking ABILIFY yourself.
- ABILIFY can be taken with or without food.
- ABILIFY tablets should be swallowed whole.
- If you miss a dose of ABILIFY, take the missed dose as soon as you remember. If it is almost time for the next dose, just skip the missed dose and take your next dose at the regular time. Do not take two doses of ABILIFY at the same time.
- If you have been prescribed ABILIFY DISCMELT, take it as follows:
  - Do not open the blister until ready to take the DISCMELT tablet.

- To remove one DISCMELT tablet, 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 DISCMELT tablet.

- If you take too much ABILIFY, call your healthcare provider or poison control center at 1-800-222-1222 right away, or go to the nearest hospital emergency room.

What should I avoid while taking ABILIFY?

- Do not drive, operate heavy machinery, or do other dangerous activities until you know how ABILIFY affects you. ABILIFY may make you drowsy.
- Avoid getting over-heated or dehydrated.
  - Do not over-exercise.
  - In hot weather, stay inside in a cool place if possible.
  - Stay out of the sun. Do not wear too much or heavy clothing.
  - Drink plenty of water.

What are the possible side effects of ABILIFY?

ABILIFY may cause serious side effects, including:

- **See "What is the most important information I should know about ABILIFY?"**
- **Stroke in elderly people (cerebrovascular problems) that can lead to death**
- **Neuroleptic malignant syndrome (NMS).** Tell your healthcare provider right away if you have some or all of the following symptoms: high fever, stiff muscles, confusion, sweating, changes in pulse, heart rate, and blood pressure. These may be symptoms of a rare and serious condition that can lead to death. Call your healthcare provider right away if you have any of these symptoms.
- **Uncontrolled body movements (tardive dyskinesia).** ABILIFY may cause movements that you cannot control in your face, tongue, or other body parts. Tardive dyskinesia may not go away, even if you stop receiving ABILIFY. Tardive dyskinesia may also start after you stop receiving ABILIFY.

- **Problems with your metabolism such as:**
  - **high blood sugar (hyperglycemia)and diabetes.** Increases in blood sugar can happen in some people who take ABILIFY. Extremely high blood sugar can lead to coma or death. If you have diabetes or risk factors for diabetes (such as being overweight or a family history of diabetes), your healthcare provider should check your blood sugar before you start ABILIFY and during your treatment.

    Call your healthcare provider if you have any of these symptoms of high blood sugar while receiving ABILIFY:

    - feel very thirsty
    - need to urinate more than usual
    - feel very hungry
    - feel weak or tired
    - feel sick to your stomach
    - feel confused, or your breath smells fruity

  - **increased fat levels (cholesterol and triglycerides) in your blood.**
  - **weight gain.** You and your healthcare provider should check your weight regularly.
- **Orthostatic hypotension (decreased blood pressure).** Lightheadedness or fainting may happen when rising too quickly from a sitting or lying position.
- **Low white blood cell count**
- **Seizures (convulsions)**
- **problems with control of your body temperature especially when you exercise a lot or are in an area that is very hot. It is important for you to drink water to avoid dehydration.** See "What should I avoid while receiving ABILIFY?"
- **difficulty swallowing that can cause food or liquid to get into your lungs.**

The most common side effects of ABILIFY in adults include:

- nausea
- vomiting
- constipation
- headache
- blurred vision
- upper respiratory illness
- dizziness
- anxiety
- insomnia
- restlessness
- inner sense of restlessness/need to move (akathisia)

The most common side effects of ABILIFY in children include:

- feeling sleepy
- headache
- vomiting
- fatigue
- increased or decreased appetite
- increased saliva or drooling
- insomnia
- nausea
- stuffy nose
- weight gain
- uncontrolled movement such as restlessness, tremor, muscle stiffness

These are not all the possible side effects of ABILIFY. For more information, ask your healthcare provider or pharmacist.

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

How should I store ABILIFY?

- Store ABILIFY at room temperature, between 68°F to 77°F (20°C to 25°C).
- 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.

Keep ABILIFY and all medicines out of the reach of children.

General information about the safe and effective use of ABILIFY.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ABILIFY for a condition for which it was not prescribed. Do not give ABILIFY to other people, even if they have the same symptoms you have. It may harm them.

This Medication Guide summarizes the most important information about ABILIFY. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about ABILIFY that was written for healthcare professionals.

For more information about ABILIFY visit www.abilify.com.

What are the ingredients in ABILIFY?

Active ingredient: aripiprazole

Inactive ingredients:

Tablets: 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: acesulfame potassium, aspartame (which contains phenylalanine), 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: disodium edetate, fructose (200 mg per mL), glycerin, dl-lactic acid, methylparaben, propylene glycol, propylparaben, sodium hydroxide, sucrose (400 mg per mL), and purified water. The oral solution is flavored with natural orange cream and other natural flavors

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

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

ABILIFY is a trademark of Otsuka Pharmaceutical Company.

03US14L-1121
03US14L-1121C

Revised: December 2014

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

/s/

MITCHELL V Mathis
12/12/2014

EXHIBIT E

VENABLE® LLP

750 E. PRATT STREET SUITE 900 BALTIMORE, MD 21202
T 410.244.7400 F 410.244.7742 www.Venable.com

Ralph S. Tyler

T 410.244.7436
F 410.244.7742
RTyler@Venable.com

January 21, 2015

Via email and First Class Mail

Elizabeth H. Dickinson, Esq., Chief Counsel
U.S. Food and Drug Administration
White Oak Building 31
10903 New Hampshire Ave.
Silver Spring, MD 20993

Re: Otsuka Pharmaceutical Co., Ltd – Abilify

Liz

Dear Ms. Dickinson:

I write on behalf of my client Otsuka Pharmaceutical Co. Ltd. ("Otsuka") to request a meeting with you to discuss an issue which arises from FDA's recent approval of Otsuka's supplemental New Drug Application for use of Abilify in the treatment of Tourette's disorder in pediatric patients. This new indication is protected by orphan drug exclusivity, with that exclusivity expiring in December 2021. Otsuka's position is that Abilify's orphan drug exclusivity has implications for approval of a generic version of Abilify and, specifically, that FDA cannot approve an ANDA for a generic version of Abilify pending the expiration of Otsuka's orphan exclusivity period. To provide context for a meeting and discussion of these issues, Otsuka's position is summarized below.

Generally, of course, generic drugs must contain the same information on their labels as the reference listed (brand-name) drug. *See* Section 505(j)(2)(A)(v). Section 505A(o), however, authorizes certain pediatric-specific exceptions to this general same labeling requirement:

> (1) General rule. – A drug for which an application has been submitted or approved under section 355(j) of this title shall not be considered ineligible for approval under that section or misbranded under section 352 of this title on the basis that the labeling of the drug omits a pediatric indication or any other aspect of labeling pertaining to pediatric use when the omitted indication or other aspect is protected by patent or by exclusivity under clause (iii) or (iv) of section 355(j)(5)(F) of this title.
>
> (2) Labeling. – Notwithstanding clauses (iii) and (iv) of section 355(j)(5)(F) of this title, the Secretary may require that the labeling of a drug approved under section 355(j)

of this title that omits a pediatric indication or other aspect of labeling as described in paragraph (1) include--

(A) a statement that, because of marketing exclusivity for a manufacturer—

(i) the drug is not labeled for pediatric use; or

(ii) in the case of a drug for which there is an additional pediatric use not referred to in paragraph (1), the drug is not labeled for the pediatric use under paragraph (1); and

(B) a statement of any appropriate pediatric contraindications, warnings, precautions, or other information that the Secretary considers necessary to assure safe use.

Thus, Section 505A(o) expressly allows pediatric information from the reference drug's label to be omitted from ANDA labeling when such information is unavailable to the ANDA sponsor due to patent protection or three-year exclusivity under Section 505(j)(5)(F)(iii) or (iv). Orphan drug exclusivity, by contrast, is granted pursuant to Section 527, and is not among the categories of protected pediatric information that Congress authorized to be omitted from a generic's label.

Because Congress in Section 505A(o) identified specific statutory exceptions to the general rule that a generic drug must bear the same label as its respective reference listed (brand) drug (*i.e.,* pediatric labeling protected by patent or three year exclusivity), those specifically identified exceptions to the general rule are an exclusive list and all other exceptions (here, pediatric labeling protected by orphan drug exclusivity) are excluded. *Expressio unius est exclusio alterius* (the expression of one thing is the exclusion of another). *See Leatherman v. Tarrant County Narcotics Intelligence and Coordination Unit*, 507 U.S. 163, 168 (1993). When, as here, Congress expressly identifies specific statutory exceptions (*i.e.*, pediatric labeling protected by patent or three-year exclusivity), the exceptions so identified are an exclusive list and all other exceptions are excluded (*e.g.*, pediatric labeling protected by orphan drug exclusivity). *See Andrus v. Glover Constr. Co.*, 446 U.S. 608, 616-617 (1980) ("Where Congress explicitly enumerates certain exceptions to a general prohibition, additional exceptions are not to be implied, in the absence of evidence of a contrary legislative intent.").

In summary, because Abilify's approved indication for the treatment of Tourette's disorder in pediatric patients is protected by orphan drug exclusivity, and FDA cannot omit pediatric information protected by orphan drug exclusivity, FDA is precluded from approving an ANDA for a generic version of Abilify until Abilify's orphan drug exclusivity period expires.

VENABLE® LLP

Because of the importance of this issue to Otsuka, I respectfully request the opportunity to meet with you. With your permission, I will call your office in a couple of days and seek to schedule a meeting.

Thank you for your consideration.

Very truly yours,

Ralph S. Tyler

EXHIBIT F

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Office of Orphan Products Development
Food and Drug Administration
10903 New Hampshire Avenue
WO32-5271
Silver Spring, MD 20993

FEB 24 2015

Otsuka Pharmaceutical Development & Commercialization, Inc.
2440 Research Blvd.
Rockville, MD 20850

Attention: David Goldberger, RPh, RAC
Vice President, Global Regulatory Affairs

Re: Orphan-drug designation # 05-2079

Dear Mr. Goldberger:

This letter refers to Otsuka Pharmaceutical Development & Commercialization, Inc.'s orphan drug aripiprazole which was designated pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bb) on January 25, 2006, for "treatment of Tourette's syndrome." We also refer to the letter from the Center for Drug Evaluation and Research dated December 12, 2014, granting marketing approval of your New Drug Applications for Abilify (aripiprazole).

This letter is to inform you that as the first sponsor of this drug to obtain marketing approval for this indication, the sponsor is entitled to seven years of orphan-drug exclusive approval pursuant to section 527 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360cc) for ***treatment of Tourette's disorder.*** The seven-year exclusive approval began on December 12, 2014, the date of approval of the New Drug Applications (NDAs 21436/S-038, 21713/S-030, 21729/S-022 & 21866/S-023). The scope of orphan-drug exclusive approval is described under 21 CFR 316.31.

As the holder of exclusivity, the sponsor is required to assure the availability of sufficient quantities of this drug to meet the needs of patients. Failure to do so could result in the withdrawal of the drug's exclusive approval as stipulated under 21 CFR 316.36(b).

Congratulations on obtaining orphan-drug exclusivity. Should you have any questions, please contact Jeff Fritsch, RPh at 301-796-8682 or alternatively at 301-796-8660.

Sincerely yours,

Gayatri Rao

Gayatri R. Rao, MD, JD
Director
Office of Orphan Products Development

EXHIBIT G

[redacted]

Attachments: Sallee Declaration March 28 2015.pdf.pdf; SALLEE PROFILE.pdf.pdf

[redacted]

From: Guinn, Patrick
Sent: Wednesday, March 18, 2015 4:53 PM
To: Bender, William
Cc: Guinn, Patrick
Subject: NDA 21436/S-038; NDA 21713/S-030; NDA 21729/S-022; NDA 21866/S-023 (Abilify Tourette's Disorder sNDA)

Dear Bill,

Re: Orphan Drug Designation # 05-2079

We are in receipt of the agency's supplemental approval letter, changing the approved indication for Abilify (aripiprazole) from an approval for use limited to pediatric patients with Tourette's Disorder to an approval for use in all patients with Tourette's Disorder, both pediatric and adult patients. We believe this change is wrong as a matter of fact, wrong as a matter of law, and should be rescinded. We hereby lodge our formal objection to the change. As the agency is well aware, the clinical trial data submitted in support of the request for a new indication for Abilify for the treatment of Tourette's Disorder was data demonstrating the safety and effectiveness of Abilify for the treatment of Tourette's Disorder in pediatric patients only; no data was submitted demonstrating safety and effectiveness in the non-pediatric adult population of patients with Tourette's Disorder. In support of our objection to the agency's broadening the approved indication from pediatric patients (an indication for which we submitted supporting clinical trial data) to an approved indication for use in the population at large (in the absence of any supporting clinical trial data demonstrating safety and effectiveness in the non-pediatric adult population), we submit the attached declaration of Dr. Floyd Sallee. Dr. Sallee is a leader in the field of treatment of Tourette's Disorder. His declaration confirms the differences between Tourette's in adult as compared to pediatric patients and also addresses the differences in medication dosing in these two distinct populations.

Regards, Patrick.

From: Bender, William [mailto:William.Bender2@fda.hhs.gov]
Sent: Wednesday, March 11, 2015 7:41 AM
To: Guinn, Patrick
Cc: Goldberger, David

Subject: RE: NDA 21436/S-038; NDA 21713/S-030; NDA 21729/S-022; NDA 21866/S-023 (Abilify Tourette's Disorder sNDA)

Good Morning Patrick,

We consider the supplemental approval to be for the treatment of Tourette's disorder in the general population.

Thank you and please let me know if you have any other questions.

-Bill

From: Guinn, Patrick [mailto:Patrick.Guinn@otsuka-us.com]
Sent: Monday, March 09, 2015 8:29 AM
To: Bender, William
Cc: Goldberger, David; Guinn, Patrick
Subject: NDA 21436/S-038; NDA 21713/S-030; NDA 21729/S-022; NDA 21866/S-023 (Abilify Tourette's Disorder sNDA)

Dear Bill,

I am writing to inquire about the revised approval letter the Division issued to Otsuka post-dated to December 12, 2014, and received by Otsuka on February 25, 2015, that includes a 'corrected statement' removing the reference to approval in the pediatric population.

Specifically, does the Division consider the supplemental approval to be for the treatment of Tourette's disorder in the general population, or is the approval limited to the pediatric population in which Otsuka demonstrated safety and efficacy?

Thank you in advance for your prompt reply.

Regards, Patrick.

Patrick F. Guinn, RAC
Director, Global Regulatory Affairs
Otsuka Pharmaceutical Development & Commercialization, Inc.

2440 Research Blvd.
Rockville, MD 20850 USA
Phone: 1-240-683-3277
Mobile: 1-301-335-2967
Email: Patrick.Guinn@otsuka-us.com

EXHIBIT H

DECLARATION OF DR. FLOYD SALLEE

1. My name is Floyd Sallee. I am over the age of 18 and am competent testify to the matters stated herein.

2. I am a graduate of Southern Illinois University (M.D. 1978) and the University of Pittsburgh (Ph.D. 1988). I am a professor of psychiatry at the University of Cincinnati Medical School. My clinical interests include Tourette's Disorder. I am Board Certified in Psychiatry, Child Psychiatry, and Clinical Pharmacology. I have been a Professor of Psychiatry and Neuroscience at the University of Cincinnati School of Medicine and have held positions of Vice Chairman and Division Chief of Child Psychiatry at Cincinnati Children's Medical Center. In addition, I have supported pediatric labeling for more than 50 marketed drugs, including Vyvanse, Adderall XR, and Concerta. For reference, my professional C.V. is attached.

3. I have many years of experience in treating patients, both children and adults, with Tourette's Disorder. I also have a great deal of experience over many years in the use of the drug aripiprazole, which Otsuka markets under the name Abilify®.

4. In 2005, I filed an application with the Food and Drug Administration ("FDA") seeking orphan drug designation for the use of aripiprazole for the treatment of Tourette's Syndrome in pediatric patients. FDA granted the requested orphan drug designation for treatment of Tourette's Syndrome. I subsequently sold the designation to Otsuka.

5. I understand that FDA has approved an indication for the use of aripiprazole in the treatment of Tourette's Disorder in the population at large (both pediatric patients and adult patients), after first approving an indication limited to the treatment of Tourette's Disorder in pediatric patients only.

6. Tourette's Disorder in adults presents in fundamentally different ways than the Disorder does in the pediatric population. The treatment of adults with Tourette's Disorder is more difficult than is the treatment of the pediatric population with the Disorder. Adults with Tourette's Disorder are commonly treatment-resistant, and the Disorder commonly presents itself with other psychiatric conditions. Effective treatment of adults often requires more intense interventions than that involved with children who have the Disorder.

7. Aripiprazole is used for the treatment of Tourette's Disorder in both the pediatric population and adults; however, the dosing in the two population groups is very different. The dose for adults is typically 20 mg. or more, a factor of two or more times than that administered to pediatric patients. In addition, pediatric patients must be started at much lower doses than adults with the dose gradually increased. Without specialized knowledge, a clinician could not treat an adult with Tourette's Disorder with aripiprazole in reliance upon a label containing dosing instructions for the pediatric population.

I declare under penalty of perjury that the foregoing is true and correct.

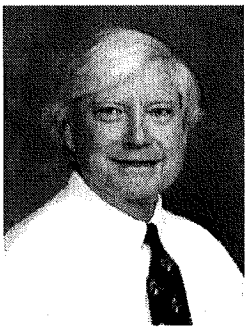
Executed on the 18th day of March, 2015.

Floyd Sallee, M.D.; Ph.D.

Department Directory Profile

Floyd Sallee, MD, PhD
Professor of Psychiatry

Stetson Building
513-558-7700
floyd.sallee@uc.edu



Interest:
Dr. Sallee's major areas of clinical interest include Tourette disorder, pediatric psychopharmacology, and ADHD. Current interests include novel GPCRs and their therapeutic potential for anxiety and obesity.

Education:
Medical Degree: Southern Illinois University, 1978

Doctoral Degree: University of Pittsburgh, 1988

Residency: University of Pittsburgh

Fellowship: University of Pittsburgh

Current Research:
National Institute of Neurological Disorders and Stroke. Attention Deficit Hyperactivity Disorder Phenotype Network: Animal Model to Clincal Trial, PI, Closed.

5-R01-NS-39087-07-A0-S0-E0 National Institute of Neurological Disorders and Stroke. Clonidine in Attention Deficit Hyperactivity Disorder, PI, Closed.

National Institute of Mental Health. Pulse Loaded IV Clomipramine in Unresponsive OCD, PI, Closed.

1-R01-MH-57471-01-A0-S0-E0 National Institute of Mental Health. Pulse Loaded, IV Clomipramine Study in Patients with Unresponsive OCD, PI, Closed.

NARSAD-06-01-A0-S0-E0 National Alliance for Research on Schizophrenia and Depression. Pulse Intravenous Clompramine in Depressed Adolescents, PI, Closed.

1 R01 MH081854-01A2 National Institute of Mental Health. Cortical Excitability: Phenotype And Biomarker In ADHD Therapy, PI, Active.

Publications

Peer Reviewed Publications (in chronological order):

Sallee, F. R., & Eaton, K. (2010). (In Press). Guanfacine extended-release for attention-deficit/hyperactivity disorder (ADHD).. Expert Opinion on Pharmacotherapy.

McGuire, J., Herman, J. P., Horn, P. S., Sallee, F. R., & Sah, R. (2010). (In Press). Enhanced fear recall and emotional arousal in rats recovering from chronic variable stress.. Physiology & Behavior.

Estes, A., McAllen, K., Parker, M. S., Sah, R., Sweatman, T., Park, E. A., Balasubramaniam, A., Sallee, F. R., Walker, M. W., & Parker, S. L. (2010). (In Press). Maintenance of Y receptor dimers in epithelial cells depends on interaction with G-protein heterotrimers.. Amino Acids.

Parker, M. S., Park, E. A., Sallee, F. R., & Parker, S. L. (2010). (In Press). Two intracellular helices of G-protein coupling receptors could generally support oligomerization and coupling with transducers.. Amino Acids.

Sah, R., Ekhator, N. N., Strawn, J. R., Sallee, F. R., Baker, D. G., Horn, P. S., & Geracioti, T. D. (2009). (In Press). Low cerebrospinal fluid neuropeptide Y concentrations in posttraumatic stress disorder.. Biological Psychiatry, 66(7), 705-7.

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