CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21-436/S017
21-713/S012
21-729/S004
21-866/S004

Trade Name: Abilify

Generic Name: Aripiprazole

Sponsor: Otsuka Pharmaceutical

Approval Date: October 29, 2007

Indications: As oral formulation for treatment of Schizophrenia in adults and adolescents aged 13-17 years. Treatment of acute manic or mixed episodes associated with Bipolar I Disorder in adults.
As an injection for treatment of adults with agitation associated with Schizophrenia or Bipolar I Disorder, manic or mixed.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-436/S017

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21-866/S004

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-436 S-017
NDA 21-713 S-012
NDA 21-729 S-004
NDA 21-866 S-004

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

Dear Dr. Mallikaarjun:

Please refer to your March 23, 2007 supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ABILIFY (aripiprazole) Tablets, ABILIFY DISCMELT Orally Disintegrating Tablets, ABILIFY Oral Solution, and ABILIFY Injection FOR INTRAMUSCULAR USE ONLY.

Your submission of September 28, 2007 to NDA 21-436 and your cross reference submission of October 4, 2007 to NDAs 21-713, 21-729, and 21-866 constituted a complete response to our action letter of September 25, 2007.

These supplemental new drug applications provide for the use of Abilify for the treatment of schizophrenia in adolescents aged 13-17.

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

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

Within 21 days of the date of this letter, submit content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical in content to the enclosed labeling text. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission **"SPL for approved supplement NDA 21-436/S-017, NDA 21-713 S-012, NDA 21-729 S-004, NDA 21-866 S-004."**

Please refer to the requests made in the cover letter of your September 28, 2007 submission –

- We agree that individual or published case reports of serious occurrences of the subsumed adverse event terms will not need to be reported to the agency according to CFR 314.80 (c)(1)(i) Post Marketing 15 day "Alert Reports".
- We hereby grant a waiver for the half-page length requirement for the Highlights Section for the PLR format label, on this sNDA and future sNDA submissions.

In addition, submit three copies of the introductory promotional materials that you propose to use for these products. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

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

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

MEDWATCH
Food and Drug Administration
5515 Security Lane
HFD-001, Suite 5100
Rockville, MD 20852

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

If you have any questions, call Keith Kiedrow, PharmD, Regulatory Project Manager, at (301) 796-1924.

Sincerely,

{See appended electronic signature page}

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

Enclosure

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

/s/

Thomas Laughren
10/29/2007 06:47:48 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-436/S017

21-713/S012

21-729/S004

21-866/S004

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-436 S-016 / S-017
NDA 21-713 S-010 / S-012
NDA 21-729 S-002 / S-004
NDA 21-866 S-003 / S-004

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

Dear Dr. Mallikaarjun:

Please refer to your March 23, 2007 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Abilify (aripiprazole) 2, 5, 10, 15, 20, and 30 mg Tablets.

Please also refer to your August 27, 2007 letters to the Abilify Discmelt Orally Disintegrating Tablets, Abilify Oral Solution, and Abilify Injection applications. These prior approval labeling supplements incorporated the NDA 21-436, S-017 submission into each respective application.

We acknowledge receipt of your submissions dated –

May 22, 2007	June 6, 2007	June 19, 2007	June 21, 2007
June 29, 2007	July 2, 2007	July 11, 2007	July 20, 2007
August 8, 2007	August 20, 2007		

These supplemental new drug applications provide for the use of Abilify for acute schizophrenia in adolescents aged 13-17.

We also acknowledge receipt of your submissions dated November 14, 2006 to Abilify Tablets, Abilify Discmelt Orally Disintegrating Tablets, Abilify Oral Solution, and Abilify Injection applications. These changes being effected labeling submissions provided for additional terms added to the adverse reactions section of labeling.

We completed our review of these applications, and they are approvable. Before these applications may be approved, however, you must review and make changes according to the recommendations contained in the enclosed printed labeling. To facilitate review of your submission, provide a highlighted or marked-up copy that shows the changes.

If additional information relating to the safety or effectiveness of these drugs becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the applications under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with this division to discuss what further steps need to be taken before the application may be approved.

These products may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if they are marketed with these changes before approval of these supplemental applications.

If you have any questions, call Keith Kiedrow, PharmD, Regulatory Project Manager, at (301) 796-1924.

Sincerely,

{See appended electronic signature page}

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

Enclosure

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

/s/

Thomas Laughren
9/25/2007 05:00:37 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-436/S017

21-713/S012

21-729/S004

21-866/S004

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

See full prescribing information for complete boxed warning.
Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. ABILIFY is not approved for the treatment of patients with dementia-related psychosis. (5.1)

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

Indications and Usage, Pediatric (13 to 17 yrs) Schizophrenia (1.1)	10/2007
Dosage and Administration, Pediatric Schizophrenia (2.1)	10/2007

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

ABILIFY is an atypical antipsychotic indicated
as oral formulations for:

- Treatment of Schizophrenia in adults and adolescents aged 13-17 years (1.1)
- Treatment of acute manic or mixed episodes associated with Bipolar I Disorder in adults (1.2)

as an injection for:

- Treatment of adults with agitation associated with Schizophrenia or Bipolar I Disorder, manic or mixed (1.3)

----------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 (2.2)	15-30 mg /day	15-30 mg /day	30 mg /day
Agitation associated with Schizophrenia or Bipolar Mania– adults (2.5)	9.75 mg /1.3 mL injected IM		30 mg /day injected IM

- ABILIFY oral formulations: Administer once daily without regard to meals (2)
- ABILIFY injection: Wait at least 2 hours between doses. Maximum daily dose 30 mg (2.3)

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

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

----------CONTRAINDICATIONS----------

Known hypersensitivity to ABILIFY (4)

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

- *Elderly patients with dementia-related psychosis* Increased incidence of cerebrovascular adverse events (eg, stroke, transient ischemic attack, including fatalities) (5.1)
- *Neuroleptic Malignant Syndrome*: Manage with immediate discontinuation and close monitoring (5.2)
- *Tardive Dyskinesia* Discontinue if clinically appropriate (5.3)
- *Hyperglycemia and Diabetes Mellitus*: Monitor glucose regularly in patients with and at risk for diabetes (5.4)
- *Orthostatic Hypotension* Use with caution in patients with known cardiovascular or cerebrovascular disease (5.5)
- *Seizures/Convulsions* Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold (5.6)
- *Potential for Cognitive and Motor Impairment* Use caution when operating machinery (5.7)
- *Suicide* Closely supervise high-risk patients (5.10)

----------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 yrs) with Schizophrenia: extrapyramidal disorder, somnolence, and tremor
- Adult patients with Bipolar Mania: constipation, akathisia, sedation, tremor, restlessness, and extrapyramidal disorder
- 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----------

- *Strong CYP3A4 or CYP2D6 inhibitors will increase* ABILIFY drug concentrations; reduce ABILIFY dose by one-half when used concomitantly (2.1, 7.1)
- *CYP3A4 inducers will decrease* ABILIFY drug concentrations; double ABILIFY dose when used concomitantly (2.1, 7.1)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 10/2007

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. ABILIFY (aripiprazole) is not approved for the treatment of patients with dementia-related psychosis. *[see WARNINGS AND PRECAUTIONS (5.1)].*

1 INDICATIONS AND USAGE

1.1 Schizophrenia

Adults

ABILIFY is indicated for acute and maintenance treatment of Schizophrenia *[see CLINICAL STUDIES (14.1)]*.

Adolescents

ABILIFY is indicated for the treatment of Schizophrenia in adolescents 13 to 17 years of age *[see CLINICAL STUDIES (14.1)]*.

1.2 Bipolar Disorder

Adults

ABILIFY is indicated for acute and maintenance treatment of manic and mixed episodes associated with Bipolar I Disorder with or without psychotic features *[see CLINICAL STUDIES (14.2)]*.

1.3 Agitation Associated with Schizophrenia or Bipolar Mania

Adults

ABILIFY Injection is indicated for the treatment of agitation associated with Schizophrenia or Bipolar Disorder, manic or mixed. "Psychomotor agitation" is defined in DSM-IV as "excessive motor activity associated with a feeling of inner tension." Patients experiencing agitation often manifest behaviors that interfere with their diagnosis and care (eg, threatening behaviors, escalating or urgently distressing behavior, or self-exhausting behavior), leading clinicians to the use of intramuscular antipsychotic medications to achieve immediate control of the *agitation [see CLINICAL STUDIES (14.3)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Schizophrenia

Usual Dose

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 not be made before 2 weeks, the time needed to achieve steady state. *[See CLINICAL STUDIES (14.1)]*.

Adolescents

The recommended target dose of ABILIFY is 10 mg/day. Aripiprazole was studied in pediatric 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)]*.

Dosage in Special Populations

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

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

Dosage adjustment for patients taking aripiprazole concomitantly with potential CYP2D6 inhibitors: When concomitant administration of potential CYP2D6 inhibitors such as quinidine, fluoxetine, or paroxetine with aripiprazole occurs, aripiprazole dose should be reduced at least to one-half of its normal dose. When the CYP2D6 inhibitor is withdrawn from the combination therapy, the aripiprazole dose should then be increased *[see DRUG INTERACTIONS (7.1)]*.

Dosage adjustment for patients taking potential CYP3A4 inducers: When a potential CYP3A4 inducer such as carbamazepine is added to aripiprazole therapy, the aripiprazole dose should be doubled. Additional dose increases should be based on clinical evaluation. When the CYP3A4 inducer is withdrawn from the combination therapy, the aripiprazole dose should be reduced to 10 mg to 15 mg *[see DRUG INTERACTIONS (7.1)]*.

Maintenance Therapy

Adults

While there is no body of evidence available to answer the question of how long a patient treated with aripiprazole should remain on it, systematic evaluation of patients with Schizophrenia who had been symptomatically stable on other antipsychotic medications for periods of 3 months or longer, were discontinued from those medications, and were then administered ABILIFY 15 mg/day and observed for relapse during a period of up to 26 weeks, has demonstrated a benefit of such maintenance treatment *[see CLINICAL STUDIES (14.1)]*. Patients should be periodically reassessed to determine the need for maintenance treatment.

Pediatric Patients

The efficacy of ABILIFY for the maintenance treatment of Schizophrenia in the pediatric population has not been evaluated.

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 Disorder

Usual Dose

Adults

In clinical trials, the starting dose was 30 mg given once a day, without regard to meals. A dose of 30 mg/day was found to be effective when administered as the tablet formulation. Approximately 15% of patients had their dose decreased to 15 mg based on assessment of tolerability. The safety of doses above 30 mg/day has not been evaluated in clinical trials.

Dosage in Special Populations

See *DOSAGE AND ADMINISTRATION (2.1)*.

Maintenance Therapy

While there is no body of evidence available to answer the question of how long a patient treated with aripiprazole should remain on it, adult patients with Bipolar I Disorder who had been symptomatically stable on ABILIFY Tablets (15 mg/day or 30 mg/day with a starting dose of 30 mg/day) for at least 6 consecutive weeks and then randomized to ABILIFY Tablets (15 mg/day or 30 mg/day) or placebo and monitored for relapse, demonstrated a benefit of such maintenance treatment *[see CLINICAL STUDIES (14.2)]*. While it is generally agreed that pharmacological treatment beyond an acute response in Mania is desirable, both for maintenance of the initial response and for prevention of new

manic episodes, there are no systematically obtained data to support the use of aripiprazole in such longer-term treatment (beyond 6 weeks). Physicians who elect to use ABILIFY for extended periods, that is, longer than 6 weeks, should periodically re-evaluate the long-term usefulness of the drug for the individual.

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

Usual Dose

Adults

The recommended dose in these patients is 9.75 mg. The effectiveness of aripiprazole injection in controlling agitation in Schizophrenia and Bipolar Mania was demonstrated over a dose range of 5.25 mg to 15 mg. No additional benefit was demonstrated for 15 mg compared to 9.75 mg. A lower dose of 5.25 mg may be considered when clinical factors warrant. If agitation warranting a second dose persists following the initial dose, cumulative doses up to a total of 30 mg/day may be given. However, the efficacy of repeated doses of aripiprazole injection in agitated patients has not been systematically evaluated in controlled clinical trials. The safety of total daily doses greater than 30 mg or injections given more frequently than every 2 hours have not been adequately evaluated in clinical trials *[see CLINICAL STUDIES (14.3)]*.

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

Administration of ABILIFY Injection

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

Table 1: ABILIFY Injection Dosing Recommendations

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

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

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

Dosage in Special Populations

See DOSAGE AND ADMINISTRATION (2.1).

2.4 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)]*.

2.5 Dosing of Orally Disintegrating Tablets

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

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

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

5 WARNINGS AND PRECAUTIONS

5.1 Use in Elderly Patients with Dementia-Related Psychosis

Increased Mortality

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

Cerebrovascular Adverse Events, Including Stroke

In placebo-controlled clinical studies (two flexible dose and one fixed dose study) of dementia-related psychosis, there was an increased incidence of cerebrovascular adverse events (eg, stroke, transient ischemic attack), including fatalities, in aripiprazole-treated patients (mean age: 84 years; range: 78-88 years). In the fixed-dose study, there was a statistically significant dose response relationship for cerebrovascular adverse events in

patients treated with aripiprazole. Aripiprazole is not approved for the treatment of patients with dementia-related psychosis *[see also BOXED WARNING]*.

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

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

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

5.2 Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) may occur with administration of antipsychotic drugs, including aripiprazole. Rare cases of NMS occurred during aripiprazole treatment in the worldwide clinical database. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

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

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

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

5.3 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.

5.4 Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. There have been few reports of hyperglycemia in patients treated with ABILIFY *[see ADVERSE REACTIONS (6.2, 6.3)]*. Although fewer patients have been treated with ABILIFY, it is not known if this more limited experience is the sole reason for the paucity of such reports. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with Schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies which did not include ABILIFY suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics included in these studies. Because ABILIFY was not marketed at the time these studies were performed, it is not known if ABILIFY is associated with this increased risk. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

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

5.5 Orthostatic Hypotension

Aripiprazole 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 patients on oral ABILIFY included (aripiprazole incidence, placebo incidence): in adults with Schizophrenia (n=926): orthostatic hypotension (1.9%, 1%), postural dizziness (0.8%, 0.7%), and syncope (0.6%, 1%); in pediatric patients 13 to 17 yrs of age with Schizophrenia (n=202): orthostatic hypotension (1.5%, 0%), postural dizziness (1.0%, 0%), and syncope (0.5%, 0%); in adults with Bipolar Mania (n=597): orthostatic hypotension (0.7%, 0%), postural dizziness (0.5%, 0.2%), and syncope (0.3%, 0.7%): and in adult patients with agitation associated with Schizophrenia or Bipolar Mania (n=501) on ABILIFY Injection included: orthostatic hypotension (0.6%, 0%), postural dizziness (0.2%, 0.5%), and syncope (0.4%, 0%).

The incidence of a significant orthostatic change in blood pressure (defined as a decrease of at least 30 mmHg in systolic blood pressure when changing from a supine to standing position) for aripiprazole was not meaningfully different from placebo (aripiprazole incidence, placebo incidence): in adult patients with Schizophrenia (14%, 12%), in pediatric patients with Schizophrenia (1%, 0%), in adults with Bipolar Mania (3%, 2%), or in adults with agitation associated with Schizophrenia or Bipolar Mania (4%, 4%).

Aripiprazole should be used with caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease, or conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications).

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

5.6 Seizures/Convulsions

In short-term placebo-controlled trials of oral aripiprazole-treated patients, seizures/convulsions occurred in 0.1% (1/926) of adult patients with Schizophrenia, in 0% (0/202) of pediatric patients (13 to 17 yrs) with Schizophrenia, in 0.3% (2/597) of adult patients with Bipolar Mania, and in 0.2% (1/501) of aripiprazole injection-treated adult patients with agitation associated with Schizophrenia or Bipolar Mania.

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

5.7 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 of patients on oral ABILIFY, somnolence (including sedation) was reported as follows (aripiprazole incidence, placebo incidence): in adult patients with Schizophrenia (10%, 8%), in pediatric patients with Schizophrenia (17%, 6%), in adult patients with Bipolar Mania, (14%, 7%), in adult patients on ABILIFY Injection with agitation associated with Schizophrenia or Bipolar Mania (9%, 6%). Somnolence (including sedation) led to discontinuation in 0.1% (1/926) of adult patients with Schizophrenia, 0.5% (1/202) pediatric patients (13 to 17 yrs) with Schizophrenia, on oral ABILIFY in short-term, placebo-controlled trials, but did not lead to discontinuation of any adult patients with Bipolar Mania or with agitation associated with Schizophrenia or Bipolar Mania.

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.

5.8 Body Temperature Regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing aripiprazole for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, (eg, exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration) *[see ADVERSE REACTIONS (6.3)]*.

5.9 Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use, including ABILIFY. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. Aripiprazole and other antipsychotic drugs should be used cautiously in patients at risk

for aspiration pneumonia *[see WARNINGS AND PRECAUTIONS (5.1) and ADVERSE REACTIONS (6.3)]*.

5.10 Suicide

The possibility of a suicide attempt is inherent in psychotic illnesses and bipolar disorder, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for ABILIFY should be written for the smallest quantity consistent with good patient management in order to reduce the risk of overdose *[see ADVERSE REACTIONS (6.2, 6.3)]*.

5.11 Use in Patients with Concomitant Illness

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

ABILIFY has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies *[see WARNINGS AND PRECAUTIONS (5.1, 5.5)]*.

6 ADVERSE REACTIONS

6.1 Overall Adverse Reactions Profile

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

- Use in Elderly Patients with Dementia-Related Psychosis *[see Boxed WARNING and WARNINGS AND PRECAUTIONS (5.1)]*
- Neuroleptic Malignant syndrome (NMS) *[see WARNINGS AND PRECAUTIONS (5.2)]*
- Tardive dyskinesia *[see WARNINGS AND PRECAUTIONS (5.3)]*
- Hyperglycemia and Diabetes Mellitus *[see WARNINGS AND PRECAUTIONS (5.4)]*
- Orthostatic Hypotension *[see WARNINGS AND PRECAUTIONS (5.5)]*
- Seizures/Convulsions *[see WARNINGS AND PRECAUTIONS (5.6)]*

- Potential for Cognitive and Motor Impairment *[see WARNINGS AND PRECAUTIONS (5.7)]*
- Body Temperature Regulation *[see WARNINGS AND PRECAUTIONS (5.8)]*
- Dysphagia *[see WARNINGS AND PRECAUTIONS (5.9)]*
- Suicide *[see WARNINGS AND PRECAUTIONS (5.10)]*
- Use in Patients with Concomitant Illness *[see WARNINGS AND PRECAUTIONS (5.11)]*

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

The most common adverse reactions in the pediatric clinical trial (≥ 10%) were extrapyramidal disorder, headache, and somnolence.

Aripiprazole has been evaluated for safety in 8456 adult patients who participated in multiple-dose, clinical trials in Schizophrenia, Bipolar Mania, and Dementia of the Alzheimer's type, and who had approximately 5635 patient-years of exposure to oral aripiprazole and 749 patients with exposure to aripiprazole injection. A total of 2442 patients were treated with oral aripiprazole for at least 180 days and 1667 patients treated with oral aripiprazole had at least 1 year of exposure.

Aripiprazole has been evaluated for safety in 281 pediatric patients (13 to 17 yrs) who participated in multiple-dose, clinical trials in Schizophrenia and who had approximately 119 patient-years of exposure to oral aripiprazole. A total of 147 pediatric patients were treated with oral aripiprazole for at least 180 days.

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

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

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

Throughout this section, adverse reactions are reported. These are adverse events that were considered to be reasonably associated with the use of ABILIFY (adverse drug reactions) based on the comprehensive assessment of the available adverse event information. A causal association for ABILIFY often cannot be reliably established in individual cases.

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

6.2 Clinical Studies Experience

Adult Patients with Schizophrenia

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

Adverse Reactions Associated with Discontinuation of Treatment

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

Commonly Observed Adverse Reactions

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

Adult Patients with Bipolar Mania

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

Adverse Reactions Associated with Discontinuation of Treatment

Overall, in patients with Bipolar Mania, there was little difference in the incidence of discontinuation due to adverse events between aripiprazole-treated (11%) and placebo-treated (9%) patients. The types of adverse events that led to discontinuation were similar between the aripiprazole and placebo-treated patients.

Commonly Observed Adverse Reactions

Commonly observed adverse events associated with the use of aripiprazole in patients with Bipolar Mania (incidence of 5% or greater and aripiprazole incidence at least twice that for placebo) are shown in Table 4.

Table 4: Commonly Observed Adverse Reactions in Short-Term, Placebo-Controlled Trials of Adult Patients with Bipolar Mania Treated with Oral ABILIFY

	Percentage of Patients Reporting Reaction	
	Aripiprazole	Placebo
Preferred Term	**(n=597)**	**(n=436)**
Constipation	13	6
Akathisia	15	3
Sedation	8	3
Tremor	7	3
Restlessness	6	3
Extrapyramidal Disorder	5	2

Less Common Adverse Reactions in Adults

Table 5 enumerates the pooled incidence, rounded to the nearest percent, of adverse reactions that occurred during acute therapy (up to 6 weeks in Schizophrenia and up to 3

weeks in Bipolar Mania), including only those reactions that occurred in 2% or more of patients treated with aripiprazole (doses ≥2 mg/day) and for which the incidence in patients treated with aripiprazole was greater than the incidence in patients treated with placebo in the combined dataset.

Table 5: Adverse Reactions in Short-Term, Placebo-Controlled Trials in Adult Patients Treated with Oral ABILIFY

	Percentage of Patients Reporting Reactions[a]	
System Organ Class	**Aripiprazole**	**Placebo**
Preferred Term	**(n=1523)**	**(n=849)**
Eye Disorders		
Blurred Vision	3	1
Gastrointestinal Disorders		
Nausea	16	12
Vomiting	12	6
Constipation	11	7
Dyspepsia	10	8
Dry Mouth	5	4
Abdominal Discomfort	3	2
Stomach Discomfort	3	2
Salivary Hypersecretion	2	1
General Disorders and Administration Site Conditions		
Fatigue	6	5
Pain	3	2
Peripheral Edema	2	1
Musculoskeletal and Connective Tissue Disorders		
Arthralgia	5	4
Pain in Extremity	4	2
Nervous System Disorders		
Headache	30	25
Dizziness	11	8
Akathisia	10	4
Sedation	7	4
Extrapyramidal Disorder	6	4
Tremor	5	3
Somnolence	5	4
Psychiatric Disorders		
Anxiety	20	17
Insomnia	19	14
Restlessness	5	3
Respiratory, Thoracic, and Mediastinal Disorders		
Pharyngolaryngeal Pain	4	3
Cough	3	2
Nasal Congestion	3	2

Table 5: Adverse Reactions in Short-Term, Placebo-Controlled Trials in Adult Patients Treated with Oral ABILIFY

	Percentage of Patients Reporting Reactions[a]	
System Organ Class	**Aripiprazole**	**Placebo**
Preferred Term	**(n=1523)**	**(n=849)**
Vascular Disorders		
Hypertension[b]	2	1

[a] Adverse reactions reported by at least 2% of patients treated with oral aripiprazole, except events which had an incidence equal to or less than placebo.
[b] Including blood pressure increased.

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

Pediatric Patients (13 to 17 years) with Schizophrenia

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

Adverse Reactions Associated with Discontinuation of Treatment

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

Commonly Observed Adverse Reactions

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

Less Common Adverse Reactions in Pediatric Patients (13 to 17 yrs) with Schizophrenia

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

Table 6: Adverse Reactions in Short-Term, Placebo-Controlled Trials in Pediatric Patients (13 to 17 yrs) Treated with Oral ABILIFY

	Percentage of Patients Reporting Reaction[a]	
System Organ Class **Preferred Term**	**Aripiprazole** **(n=202)**	**Placebo** **(n=100)**
Gastrointestinal Disorders		
Nausea	9	6
Constipation	2	1
Diarrhea	2	0
Dry Mouth	2	1
Salivary Hypersecretion	2	1
General Disorders and Administration Site Conditions		
Fatigue	3	1
Infections and Infestations		
Nasopharyngitis	5	4
Metabolism and Nutrition Disorders		
Increased Appetite	3	0
Nervous System Disorders		
Extrapyramidal Disorder	17	5
Somnolence	16	6
Headache	13	10
Akathisia	8	5
Tremor	7	2
Dizziness	5	3
Dystonia	2	0
Skin and Subcutaneous Tissue Disorders		
Rash	2	0

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

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

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

Adverse Reactions Associated with Discontinuation of Treatment

Overall, in patients with agitation associated with Schizophrenia or Bipolar Mania, there was little difference in the incidence of discontinuation due to adverse events between aripiprazole-treated (0.8%) and placebo-treated (0.5%) patients.

Commonly Observed Adverse Reactions

There was one commonly observed adverse reaction (nausea) associated with the use of aripiprazole injection in patients with agitation associated with Schizophrenia and Bipolar

Mania (incidence of 5% or greater and aripiprazole incidence at least twice that for placebo).

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

Table 7 enumerates the pooled incidence, rounded to the nearest percent, of adverse reactions that occurred during acute therapy (24 hour), including only those adverse reactions that occurred in 2% or more of patients treated with aripiprazole injection (doses ≥5.25 mg/day) and for which the incidence in patients treated with aripiprazole injection was greater than the incidence in patients treated with placebo in the combined dataset.

Table 7: Adverse Reactions in Short-Term, Placebo-Controlled Trials in Patients Treated with ABILIFY Injection

	Percentage of Patients Reporting Event[a]	
System Organ Class **Preferred Term**	**Aripiprazole (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 aripiprazole injection, except the events which had an incidence equal to or less than placebo.

Dose-Related Adverse Reactions

Schizophrenia

Dose response relationships for the incidence of treatment-emergent adverse events were evaluated from four trials in adult patients with Schizophrenia comparing various fixed doses (2 mg/day, 5 mg/day, 10 mg/day, 15 mg/day, 20 mg/day, and 30 mg/day) of oral aripiprazole to placebo. This analysis, stratified by study, indicated that the only adverse reaction to have a possible dose response relationship, and then most prominent only with

30 mg, was somnolence [including sedation]; (incidences were placebo, 7.1%; 10 mg, 8.5%; 15 mg, 8.7%; 20 mg, 7.5%; 30 mg, 12.6%).

In the study of pediatric patients (13 to 17 years of age) with Schizophrenia, 3 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%).

Extrapyramidal Symptoms

In short-term, placebo-controlled trials in Schizophrenia in adults, the incidence of reported EPS-related events, excluding events related to akathisia, for aripiprazole-treated patients was 13% vs. 12% for placebo; and the incidence of akathisia-related events for aripiprazole-treated patients was 8% vs. 4% for placebo. In the short-term, placebo-controlled trial of Schizophrenia in pediatric (13-17 years) patients, the incidence of reported EPS-related events, excluding events related to akathisia, for aripiprazole-treated patients was 25% vs. 7% for placebo; and the incidence of akathisia-related events for aripiprazole-treated patients was 9% vs. 6% for placebo. 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 aripiprazole-treated patients was 15% vs. 8% for placebo and the incidence of akathisia-related events for aripiprazole-treated patients was 15% vs. 4% for placebo.

Objectively collected data from those trials was collected on the Simpson Angus Rating Scale (for EPS), the Barnes Akathisia Scale (for akathisia), and the Assessments of Involuntary Movement Scales (for dyskinesias). In the adult Schizophrenia trials, the objectively collected data did not show a difference between aripiprazole and placebo, with the exception of the Barnes Akathisia Scale (aripiprazole, 0.08; placebo, -0.05). In the pediatric (13 to 17 yrs) Schizophrenia trial, the objectively collected data did not show a difference between aripiprazole and placebo, with the exception of the Simpson Angus Rating Scale (aripiprazole, 0.24; placebo, -0.29). In the Bipolar Mania trials, the Simpson Angus Rating Scale and the Barnes Akathisia Scale showed a significant difference between aripiprazole and placebo (aripiprazole, 0.61; placebo, 0.03 and aripiprazole, 0.25; placebo, -0.06). Changes in the Assessments of Involuntary Movement Scales were similar for the aripiprazole and placebo groups.

Similarly, in a long-term (26-week), placebo-controlled trial of Schizophrenia, objectively collected data on the Simpson Angus Rating Scale (for EPS), the Barnes

Akathisia Scale (for akathisia), and the Assessments of Involuntary Movement Scales (for dyskinesias) did not show a difference between aripiprazole and placebo.

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

Laboratory Test Abnormalities

A between group comparison for 3-week to 6-week, placebo-controlled trials revealed no medically important differences between the aripiprazole and placebo groups in the proportions of patients experiencing potentially clinically significant changes in routine serum chemistry, hematology, or urinalysis parameters. Similarly, there were no aripiprazole/placebo differences in the incidence of discontinuations for changes in serum chemistry, hematology, or urinalysis.

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

Weight Gain

In 4-week to 6- week trials in adults with Schizophrenia, there was a slight difference in mean weight gain between aripiprazole and placebo patients (+0.7 kg vs. -0.05 kg, respectively) and also a difference in the proportion of patients meeting a weight gain criterion of ≥7% of body weight [aripiprazole (8%) compared to placebo (3%)]. In a 6-week trial in pediatric patients (13 to 17 yrs) with Schizophrenia, there was a slight difference in mean weight gain between aripiprazole and placebo patients (+0.13 kg vs. -0.83 kg, respectively) and also a difference in the proportion of patients meeting a weight gain criterion of ≥7% of body weight [aripiprazole (5%) compared to placebo (1%)]. In 3-week trials in adults with Mania, the mean weight gain for aripiprazole and placebo patients was 0.0 kg vs. -0.2 kg, respectively. The proportion of patients meeting a weight gain criterion of ≥7% of body weight was aripiprazole (3%) compared to placebo (2%).

Table 8 provides the weight change results from a long-term (26-week), placebo-controlled study of aripiprazole, both mean change from baseline and proportions of patients meeting a weight gain criterion of ≥7% of body weight relative to baseline, categorized by BMI at baseline. Although there was no mean weight increase, the aripiprazole group tended to show more patients with a ≥7% weight gain.

Table 8: Weight Change Results Categorized by BMI at Baseline: Placebo-Controlled Study in Schizophrenia, Safety Sample

	BMI <23		BMI 23-27		BMI >27	
	Placebo (n=54)	Aripiprazole (n=59)	Placebo (n=48)	Aripiprazole (n=39)	Placebo (n=49)	Aripiprazole (n=53)
Mean change from baseline (kg)	-0.5	-0.5	-0.6	-1.3	-1.5	-2.1
% with ≥7% increase BW	3.7%	6.8%	4.2%	5.1%	4.1%	5.7%

Table 9 provides the weight change results from a long-term (52-week) study of aripiprazole, both mean change from baseline and proportions of patients meeting a weight gain criterion of ≥7% of body weight relative to baseline, categorized by BMI at baseline:

Table 9: Weight Change Results Categorized by BMI at Baseline: Active-Controlled Study in Schizophrenia, Safety Sample

	BMI <23 (n=314)	BMI 23-27 (n=265)	BMI >27 (n=260)
Mean change from baseline (kg)	2.6	1.4	-1.2
% with ≥7% increase BW	30%	19%	8%

ECG Changes

Between group comparisons for a pooled analysis of placebo-controlled trials in patients with Schizophrenia or Bipolar Mania, revealed no significant differences between oral aripiprazole and placebo in the proportion of patients experiencing potentially important changes in ECG parameters. Aripiprazole was associated with a median increase in heart rate of 5 beats per minute compared to a 1 beat per minute increase among placebo patients.

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

Additional Findings Observed in Clinical Trials

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

The adverse reactions reported in a 26-week, double-blind trial comparing oral ABILIFY and placebo in patients with Schizophrenia were generally consistent with those reported in the short-term, placebo-controlled trials, except for a higher incidence of tremor [8% (12/153) for ABILIFY vs. 2% (3/153) for placebo]. In this study, the majority of the cases of tremor were of mild intensity (8/12 mild and 4/12 moderate), occurred early in therapy (9/12 ≤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 for ABILIFY was 5% (40/859). A similar profile was observed in a long-term study in bipolar disorder.

Other Adverse Reactions Observed During the Premarketing Evaluation of Aripiprazole

Following is a list of MedDRA terms that reflect adverse reactions as defined in *ADVERSE REACTIONS (6.1)* reported by patients treated with oral aripiprazole at multiple doses ≥2 mg/day during any phase of a trial within the database of 8456 adult patients. All events assessed as possible adverse drug reactions have been included with the exception of more commonly occurring events. In addition, medically/clinically meaningful adverse reactions, particularly those that are likely to be useful to the prescriber or that have pharmacologic plausibility, have been included. Events already listed in Tables 3, 4, or 5, other parts of *ADVERSE REACTIONS (6)*, or those considered in *WARNINGS AND PRECAUTIONS (5)* have been excluded. Although the reactions reported occurred during treatment with aripiprazole, they were not necessarily caused by it.

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

Adults - Oral Administration

Blood and Lymphatic System Disorders:

≥*1/1000 patients and <1/100 patients* - leukopenia; <*1/1000 patients* - neutropenia, thrombocytopenia, agranulocytosis, idiopathic thrombocytopenic purpura

Cardiac Disorders:

≥*1/1000 patients and <1/100 patients* - cardiopulmonary failure, bradycardia, cardio-respiratory arrest, myocardial infarction, atrial fibrillation, angina pectoris, bundle branch block; <*1/1000 patients* - atrial flutter, atrioventricular block, ventricular tachycardia, complete atrioventricular block, supraventricular tachycardia

Eye Disorders:

<*1/1000 patients* - eyelid edema, photophobia, diplopia

Gastrointestinal Disorders:

≥*1/1000 patients and <1/100 patients* - dysphagia, gastroesophageal reflux disease, gastrointestinal hemorrhage, ulcer, esophagitis; <*1/1000 patients* - swollen tongue, pancreatitis

General Disorders and Administration Site Conditions:

≥*1/100 patients* - asthenia, pyrexia, ≥*1/1000 patients and <1/100 patients* - mobility decreased; <*1/1000 patients* - hypothermia

Hepatobiliary Disorders:

≥*1/1000 patients and <1/100 patients* - cholecystitis; <*1/1000 patients* - cholelithiasis, hepatitis, jaundice

Injury, Poisoning, and Procedural Complications:

≥*1/100 patients* - fall; <*1/1000 patients* - self mutilation, heat stroke

Investigations:

≥*1/100 patients* - creatine phosphokinase increased; ≥*1/1000 patients and <1/100 patients* - hepatic enzyme increased, blood urea increased, blood bilirubin increased, blood creatinine increased, electrocardiogram QT corrected interval prolonged; <*1/1000 patients* - blood lactate dehydrogenase increased, glycosylated hemoglobin increased, GGT increased

Metabolism and Nutrition Disorders:

≥*1/1000 patients and <1/100 patients* - anorexia, hyperlipidemia

Musculoskeletal and Connective Tissue Disorders:

≥*1/100 patients* - muscle spasms, myalgia, muscle rigidity; <*1/1000 patients* - rhabdomyolysis

Nervous System Disorders:

≥*1/100 patients* - coordination abnormal, parkinsonism; ≥*1/1000 patients and <1/100 patients* - speech disorder, cogwheel rigidity, memory impairment,

cerebrovascular accident, hypokinesia, tardive dyskinesia, hypotonia, hypertonia, akinesia, myoclonus; *<1/1000 patients* - bradykinesia, Grand Mal convulsion, choreoathetosis

Psychiatric Disorders:

≥1/100 patients - agitation, irritability, suicidal ideation, aggression; *≥1/1000 patients and <1/100 patients* - excitability, libido decreased, hostility, suicide attempt, libido increased, anger, delirium, completed suicide; *<1/1000 patients* - psychomotor agitation, anorgasmia, homicidal ideation, tic, premature ejaculation

Renal and Urinary Disorders:

≥1/1000 patients and <1/100 patients - urinary retention, polyuria; *<1/1000 patients* - nocturia

Reproductive System and Breast Disorders:

≥1/1000 patients and <1/100 patients - erectile dysfunction, amenorrhea, menstruation irregular; *<1/1000 patients* - gynaecomastia, priapism, breast pain, galactorrhea

Respiratory, Thoracic, and Mediastinal Disorders:

≥1/100 patients - dyspnea; *≥1/1000 patients and <1/100 patients* - pneumonia aspiration, respiratory distress; *<1/1000 patients* - pulmonary embolism, asphyxia

Skin and Subcutaneous Tissue Disorders:

≥1/100 patients - hyperhydrosis; *≥1/1000 patients and <1/100 patients* - erythema, pruritus, ecchymosis, face edema, photosensitivity reaction, alopecia; *<1/1000 patients* - urticaria

Vascular Disorders:

≥1/100 patients - hypotension*; ≥1/1000 patients and <1/100 patients* - deep vein thrombosis, phlebitis; *<1/1000 patients* - shock, thrombophlebitis

Pediatric Patients - Oral Administration

All adverse reactions observed in the pooled database of 281 pediatric patients aged 13 to 17 years were also observed in the adult population. Additional adverse reactions observed in the pediatric population are listed below.

Investigations:

≥1/100 patients - blood insulin increased

Nervous System Disorders:

≥1/1000 patients and <1/100 patients - sleep talking, psychomotor skills impaired

Skin and Subcutaneous Tissue Disorders:

≥1/1000 patients and <1/100 patients - hirsutism

Adults - Intramuscular Injection

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

General Disorders and Administration Site Conditions:

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

6.3 Postmarketing Experience

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

7 DRUG INTERACTIONS

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

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

7.1 Potential for Other Drugs to Affect ABILIFY

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

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

Ketoconazole and Other CYP3A4 Inhibitors

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

Quinidine and Other CYP2D6 Inhibitors

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

Carbamazepine and Other CYP3A4 Inducers

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

7.2 Potential for ABILIFY to Affect Other Drugs

Aripiprazole is unlikely to cause clinically important pharmacokinetic interactions with drugs metabolized by cytochrome P450 enzymes. In *in vivo* studies, 10 mg/day to 30 mg/day doses of aripiprazole had no significant effect on metabolism by CYP2D6 (dextromethorphan), CYP2C9 (warfarin), CYP2C19 (omeprazole, warfarin), and

CYP3A4 (dextromethorphan) substrates. Additionally, aripiprazole and dehydro-aripiprazole did not show potential for altering CYP1A2-mediated metabolism *in vitro*.

Alcohol

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

7.3 Drugs having No Clinically Important Interactions with ABILIFY

Famotidine

Coadministration of aripiprazole (given in a single dose of 15 mg) with a 40 mg single dose of the H_2 antagonist famotidine, a potent gastric acid blocker, decreased the solubility of aripiprazole and, hence, its rate of absorption, reducing by 37% and 21% the Cmax of aripiprazole and dehydro-aripiprazole, respectively, and by 13% and 15%, respectively, the extent of absorption (AUC). No dosage adjustment of aripiprazole is required when administered concomitantly with famotidine.

Valproate

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

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

Lithium

A pharmacokinetic interaction of aripiprazole with lithium is unlikely because lithium is not bound to plasma proteins, is not metabolized, and is almost entirely excreted unchanged in urine. Coadministration of therapeutic doses of lithium (1200-1800 mg/day) for 21 days with aripiprazole (30 mg/day) did not result in clinically significant

changes in the pharmacokinetics of aripiprazole or its active metabolite, dehydro-aripiprazole (Cmax and AUC increased by less than 20%). No dosage adjustment of aripiprazole is required when administered concomitantly with lithium.

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

Dextromethorphan

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

Warfarin

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

Omeprazole

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

Lorazepam

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

with the combination as compared to that observed with lorazepam alone *[see WARNINGS AND PRECAUTIONS (5.5)]*.

8 USE IN SPECIFIC POPULATIONS

In general, no dosage adjustment for ABILIFY is required on the basis of a patient's age, gender, race, smoking status, hepatic function, or renal function *[see DOSAGE AND ADMINISTRATION (2.1)]*.

8.1 Pregnancy

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

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

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

Pregnant rabbits were treated with oral doses of 10 mg/kg/day, 30 mg/kg/day, and 100 mg/kg/day (2 times, 3 times, and 11 times human exposure at MRHD based on AUC and 6 times, 19 times, and 65 times the MRHD based on mg/m^2) of aripiprazole during the

period of organogenesis. Decreased maternal food consumption and increased abortions were seen at 100 mg/kg. Treatment caused increased fetal mortality (100 mg/kg), decreased fetal weight (30 mg/kg and 100 mg/kg), increased incidence of a skeletal abnormality (fused sternebrae at 30 mg/kg and 100 mg/kg), and minor skeletal variations (100 mg/kg).

In pregnant rabbits receiving aripiprazole injection intravenously (3 mg/kg/day, 10 mg/kg/day, and 30 mg/kg/day) during the period of organogenesis, the highest dose, which caused pronounced maternal toxicity, resulted in decreased fetal weight, increased fetal abnormalities (primarily skeletal), and decreased fetal skeletal ossification. The fetal no-effect dose was 10 mg/kg, which produced 15 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 with oral doses of 3 mg/kg/day, 10 mg/kg/day , and 30 mg/kg/day (1 times, 3 times, and 10 times the MRHD on a mg/m^2 basis) of aripiprazole perinatally and postnatally (from day 17 of gestation through day 21 postpartum), slight maternal toxicity and slightly prolonged gestation were seen at 30 mg/kg. An increase in stillbirths and decreases in pup weight (persisting into adulthood) and survival were seen at this dose.

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

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

8.2 Labor and Delivery

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

Safety and effectiveness in pediatric patients with Bipolar Mania or agitation associated with Schizophrenia or Bipolar Mania have not been established.

Safety and effectiveness in pediatric patients with Schizophrenia were established in a 6-week, placebo-controlled clinical trial in 202 pediatric patients aged 13 to 17 years. *[See INDICATIONS AND USAGE (1.1), DOSAGE AND ADMINISTRATION (2.1), ADVERSE REACTIONS (6.2), and CLINICAL STUDIES (14.1).]*

The pharmacokinetics of aripiprazole and dehydro-aripiprazole in pediatric patients 13 to 17 years of age were similar to those in adults after correcting for the differences in body weights.

8.5 Geriatric Use

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

Of the 8456 patients treated with oral aripiprazole in clinical trials, 1000 (12%) were ≥65 years old and 794 (9%) were ≥75 years old. The majority (87%) of the 1000 patients were diagnosed with dementia of the Alzheimer's type.

Placebo-controlled studies of oral aripiprazole in Schizophrenia or Bipolar Mania did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

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

Studies of elderly patients with psychosis associated with Alzheimer's disease have suggested that there may be a different tolerability profile in this population compared to younger patients with Schizophrenia *[see also BOXED WARNING and WARNINGS AND PRECAUTIONS (5.1)]*. The safety and efficacy of ABILIFY in the treatment of patients with psychosis associated with Alzheimer's disease has not been established. If the prescriber elects to treat such patients with ABILIFY, vigilance should be exercised.

8.6 Renal Impairment

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

8.7 Hepatic Impairment

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

8.8 Gender

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

8.9 Race

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

8.10 Smoking

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

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

ABILIFY (aripiprazole) is not a controlled substance.

9.2 Abuse and Dependence

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

10 OVERDOSAGE

MedDRA terminology has been used to classify the adverse events.

10.1 Human Experience

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

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

10.2 Management of Overdosage

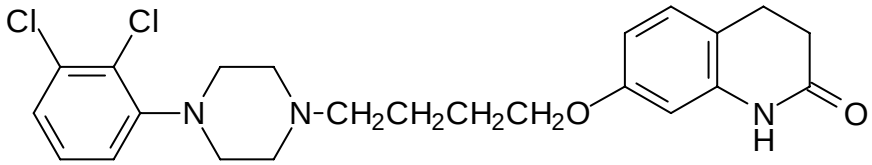
No specific information is available on the treatment of overdose with aripiprazole. An electrocardiogram should be obtained in case of overdosage and if QT interval prolongation is present, cardiac monitoring should be instituted. Otherwise, management of overdose should concentrate on supportive therapy,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

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

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 150 mg/mL of sulfobutylether β-cyclodextrin (SBECD), tartaric acid, sodium hydroxide, and water for injection.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

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

12.3 Pharmacokinetics

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

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

ORAL ADMINISTRATION

Absorption

Tablet: Aripiprazole is well absorbed after administration of the tablet, with peak plasma concentrations occurring within 3 hours to 5 hours; the absolute oral bioavailability of the tablet formulation is 87%. ABILIFY can be administered with or without food. Administration of a 15 mg ABILIFY Tablet with a standard high-fat meal did not significantly affect the 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 (2.3)]*. 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.

Approximately 8% of Caucasians lack the capacity to metabolize CYP2D6 substrates and are classified as poor metabolizers (PM), whereas the rest are extensive metabolizers (EM). PMs have about an 80% increase in aripiprazole exposure and about a 30% decrease in exposure to the active metabolite compared to EMs, resulting in about a 60% higher exposure to the total active moieties from a given dose of aripiprazole compared to EMs. Coadministration of ABILIFY with known inhibitors of CYP2D6, such as quinidine or fluoxetine in EMs, approximately doubles aripiprazole plasma exposure, and dose adjustment is needed *[see DRUG INTERACTIONS (7.1)]*. The mean elimination half-lives are about 75 hours and 146 hours for aripiprazole in EMs and PMs, respectively. Aripiprazole does not inhibit or induce the CYP2D6 pathway.

Following a single oral dose of [^{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.

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 and in Sprague-Dawley (SD) and F344 rats. Aripiprazole was administered for 2 years in the diet at doses of 1 mg/kg/day, 3 mg/kg/day, 10 mg/kg/day, and 30 mg/kg/day to ICR mice and 1 mg/kg/day, 3 mg/kg/day, and 10 mg/kg/day to F344 rats (0.2 times to 5 times and 0.3 times to 3 times the maximum recommended human dose [MRHD] based on mg/m^2, respectively). In addition, SD rats were dosed orally for 2 years at 10 mg/kg/day, 20 mg/kg/day, 40 mg/kg/day, and 60 mg/kg/day (3 times to 19 times the MRHD based on mg/m^2). Aripiprazole did not induce tumors in male mice or rats. In female mice, the incidences of pituitary gland adenomas and mammary gland adenocarcinomas and adenoacanthomas were increased at dietary doses of 3 mg/kg/day to 30 mg/kg/day (0.1 times to 0.9 times human exposure at MRHD based on AUC and 0.5 times to 5 times the MRHD based on 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 mg/kg/day, 6 mg/kg/day, and 20 mg/kg/day (0.6 times, 2 times, and 6 times the maximum recommended human dose [MRHD] on a mg/m^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 mg/kg and 20 mg/kg and decreased fetal weight was seen at 20 mg/kg.

Male rats were treated with oral doses of 20 mg/kg/day, 40 mg/kg/day, and 60 mg/kg/day (6 times, 13 times, and 19 times the MRHD on a mg/m^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 mg/kg and 60 mg/kg, but no impairment of fertility was seen.

13.2 Animal Toxicology and/or Pharmacology

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

14 CLINICAL STUDIES

14.1 Schizophrenia

Adult

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

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

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

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

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

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

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

Thus, the efficacy of 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.

Pediatric

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, 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.

14.2 Bipolar Disorder

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

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

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

A trial was conducted in patients meeting DSM-IV criteria for Bipolar I Disorder with a recent manic or mixed episode who had been stabilized on open-label ABILIFY and who had maintained a clinical response for at least 6 weeks. The first phase of this trial was an open-label stabilization period in which inpatients and outpatients were clinically stabilized and then maintained on open-label ABILIFY (15 mg/day or 30 mg/day, with a starting dose of 30 mg/day) for at least 6 consecutive weeks. One hundred sixty-one

outpatients were then randomized in a double-blind fashion, to either the same dose of ABILIFY they were on at the end of the stabilization and maintenance period or placebo and were then monitored for manic or depressive relapse. During the randomization phase, ABILIFY was superior to placebo on time to the number of combined affective relapses (manic plus depressive), the primary outcome measure for this study. The majority of these relapses were due to manic rather than depressive symptoms. There is insufficient data to know whether ABILIFY is effective in delaying the time to occurrence of depression in patients with Bipolar I Disorder.

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

14.3 Agitation Associated with Schizophrenia or Bipolar Mania

The efficacy of intramuscular aripiprazole for injection for the treatment of agitation was established in three short-term (24 hour), placebo-controlled trials in agitated inpatients from two diagnostic groups: Schizophrenia and Bipolar I Disorder (manic or mixed episodes, with or without psychotic features). Each of the trials included a single active comparator treatment arm of either haloperidol injection (Schizophrenia studies) or lorazepam injection (Bipolar Mania study). Patients could receive up to three injections during the 24-hour treatment periods; however, patients could not receive the second injection until after the initial 2-hour period when the primary efficacy measure was assessed. Patients enrolled in the trials needed to be: (1) judged by the clinical investigators as clinically agitated and clinically appropriate candidates for treatment with intramuscular medication, and (2) exhibiting a level of agitation that met or exceeded a threshold score of ≥15 on the five items comprising the Positive and Negative Syndrome Scale (PANSS) Excited Component (ie, poor impulse control, tension, hostility, uncooperativeness, and excitement items) with at least two individual item scores ≥4 using a 1-7 scoring system (1 = absent, 4 = moderate, 7 = extreme). In the studies, the mean baseline PANSS Excited Component score was 19, with scores ranging from 15 to 34 (out of a maximum score of 35), thus suggesting predominantly moderate levels of agitation with some patients experiencing mild or severe levels of agitation. The primary efficacy measure used for assessing agitation signs and symptoms in these trials was the change from baseline in the PANSS Excited Component at 2 hours post-injection. A key secondary measure was the Clinical Global Impression of Improvement (CGI-I) Scale. The results of the trials follow:

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

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

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

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

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

ABILIFY® (aripiprazole) Tablets have markings on one side and are available in the strengths and packages listed in Table 10.

Table 10: 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	"A-009"	Bottle of 30	59148-009-13

Table 10: ABILIFY Tablet Presentations

Tablet Strength	Tablet Color/Shape	Tablet Markings	Pack Size	NDC Code
	round	and "15"	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
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 11.

Table 11: 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 25º C (77º F); excursions permitted between 15º C to 30º C (59º F to 86º F) [see USP Controlled Room Temperature].

Oral Solution

Store at 25° C (77° F); excursions permitted between 15º C to 30º C (59º F to 86º 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 25º C (77º F); excursions permitted between 15° C to 30º C (59° F to 86º 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

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

Use of Orally Disintegrating Tablet

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

Interference with Cognitive and Motor Performance

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

Pregnancy

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

Nursing

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

Concomitant Medication

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

Alcohol

Patients should be advised to avoid alcohol while taking ABILIFY.

Heat Exposure and Dehydration

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

Sugar Content

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

Phenylketonurics

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

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

Orally Disintegrating Tablets, Oral Solution, and Injection manufactured by Bristol-Myers Squibb Company, Princeton, NJ 08543 USA

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

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

US Patent Nos: 5,006,528; 6,977,257; and 7,115,587

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-436/S017

21-713/S012

21-729/S004

21-866/S004

OFFICE DIRECTOR MEMO

M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: September 25, 2007

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

SUBJECT: Recommendation for approvable actions for Abilify Pediatric Supplements for schizophrenia

TO: File NDAs 21-436/S-017 (Abilify tabs), 21-713/S-012 (oral solution), 21-729/S-004 (ODT), and 21-866/S-004 (IM)
[Note: This overview should be filed with the 3-23-07 original submission of these supplements.]

1.0 BACKGROUND

Abilify (aripiprazole) is an atypical antipsychotic (5HT2 antagonist and D2 receptor partial agonist) that is approved for both schizophrenia and bipolar disorder in adults (mania and mixed episodes), both acute and maintenance therapy for both. We issued a written request (WR) for both schizophrenia and mania (2-11-03), and these supplements are a partial response to that WR. The 3-23-07 response includes the results from a single acute study in schizophrenia (Study 31-03-239), longer-term safety data from open-label Study 31-03-241, and also pediatric tolerability and PK data from Study 31-03-238.

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. We held a preNDA meeting with the sponsor on 1-18-07. The labeling included with this supplement is in PLR format, and so this re-formatted labeling was also included within the scope of our review.

2.0 CHEMISTRY

The only CMC issues requiring review were the labeling and environmental assessment. The minor labeling issues have been addressed, and the sponsor sought and was granted a categorical exclusion.

3.0 PHARMACOLOGY

The only pharm/tox issue for consideration was the re-formatted labeling, and this has been addressed.

4.0 BIOPHARMACEUTICS

OCP has considered the pk data derived from this program sufficient to support these supplements, including the proposed labeling. They determined that AUC and Cmax appear to be linear in pediatric patients. However, they have made some slight modifications to labeling.

5.0 CLINICAL DATA

5.1 Efficacy Data

Our efficacy review focused on a single short-term, multicenter, double-blind, parallel group, randomized, efficacy and safety study in adolescent patients (ages 13-17) with schizophrenia (Study 31-03-239).

5.1.1 Study 31-03-239 (Acute Schizophrenia)

This was a 6-week placebo-controlled study in adolescent patients (ages 13-17) with schizophrenia. It was conducted at multiple international sites and also the US (n=141 total centers). Patients could be inpatients or outpatients. N=294 patients (in the ITT dataset) were randomized 1:1:1 to 3 treatment groups: aripiprazole 10 mg/day (n=99); aripiprazole 30 mg/day (n=97); placebo (n=98). Roughly 85% of patients completed the study (with roughly comparable rates for all 3 groups). Patients were roughly half male, about 60% Caucasian, and the mean age was 15.5 years. The primary endpoint was change from baseline to endpoint on the PANSS total score, and the primary analysis was ANCOVA (LOCF). The Hochberg procedure was used to correct for multiple comparisons. Both dose groups were superior to placebo (p=0.006 for 30 mg and p=0.041 for 10 mg), with only a slight numerical superiority for the 30 mg dose over the 10 mg dose at endpoint: change from baseline of -28.6 for 30 mg vs -26.7 for 10 mg vs -21.2 for placebo). However, weekly data did suggest an earlier onset of effect in the 30 mg group vs the 10 mg group. The placebo effect was surprisingly large for this study. No endpoints were designated as key secondary endpoints and no multiple comparison procedure was planned for secondary endpoints. Therefore, I will not comment further on secondary endpoints. Subgroup analyses based on gender and race for this study generally suggested that the positive results were seen across subgroups. Drs. Zhang, Chen, and Mathis all considered this a positive study, and I agree.

5.1.2 Summary of Efficacy

There is unanimous agreement within the review team on the positive outcome for this study. As noted, there was no clear indication of greater efficacy for the higher dose compared to the lower dose. The sponsor has proposed language suggesting that

" however, we disagree. We will propose labeling ----------

5.2 Safety Data

Safety data for these supplements were derived from the 3 trials noted above, i.e., a single acute study in schizophrenia (31-03-239), a longer-term open-label study (31-03-241), and a pediatric tolerability and PK study (31-03-238). There were roughly 200 pediatric patients exposed to aripiprazole in study 239, with roughly 1/3 extending beyond 42 days into the open label study. There was one clearly accidental death in an aripiprazole-exposed patient in study 241. There were several serious adverse events, the majority of which represented a worsening of psychiatric symptoms. Overall, the profile of common and drug-related adverse events included events already well-recognized for aripiprazole in adults, i.e., EPS, somnolence, and GI symptoms, with slightly higher rates for some of these in pediatric patients compared to adults. Of note, there were no clear metabolic or growth effects, no laboratory effects, and if anything, a decrease in QTc. I agree with Drs. Mathis and Zhang that these adverse events can be adequately addressed in labeling.

5.3 Clinical Sections of Labeling

We have made a number of modifications to the sponsor's proposed labeling, and have asked the sponsor to make a number of changes, and in some cases, provide new information.

6.0 WORLD LITERATURE

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

7.0 FOREIGN REGULATORY ACTIONS

To my knowledge, aripiprazole is not approved anywhere at this time for the treatment of schizophrenia or bipolar disorder in pediatric patients.

8.0 DSI INSPECTIONS

Inspections were conducted at 2 sites, and data from these sites were deemed to be acceptable.

9.0 LABELING AND APPROVABLE LETTER

9.1 Labeling

We have included a modified version of labeling with the approvable letter.

9.2 Foreign Labeling

Aripiprazole is not approved anywhere at this time for the treatment of schizophrenia or bipolar disorder in pediatric patients.

9.3 Approvable Letter

The approvable letter includes our proposed labeling.

10.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Otsuka has submitted sufficient data to support the conclusion that aripiprazole is effective and acceptably safe in the treatment of adolescent patients with schizophrenia. However, before we can take an approval action, we need to reach agreement on labeling. Thus, we will issue the attached approvable letter along with our proposal for labeling.

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

/s/

Thomas Laughren
9/25/2007 04:33:34 PM
MEDICAL OFFICER

MEMORANDUM

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

DATE: 13 September 2007

FROM: Mitchell V. Mathis, M.D.
Deputy Director
Division of Psychiatry Products, HFD-130

TO: File NDA 21-436 SE5 017; 21-713 SE 012; 21-729 SE 004; 21-866 SE 004

SUBJECT: Recommendation of Approval Action for aripiprazole (Abilify®) for the Treatment of Schizophrenia in Pediatric Patients (efficacy supplement and partial response to Pediatric Written Request)

1 BACKGROUND AND REGULATORY HISTORY

The mechanism of action of aripiprazole differs from that of other currently marketed typical and atypical antipsychotics in that its effect is mediated through a combination of partial agonism/antagonism at dopamine D_2 and serotonin 5-HT_{1A} receptors, and antagonism at serotonin 5-HT_2 receptors. Aripiprazole is approved for the acute and maintenance treatment of schizophrenia in adults, the short-term treatment of acute manic episodes associated with Bipolar I Disorder in adults, and for the maintenance treatment of Bipolar I Disorder in adults. In this application, Otsuka Pharmaceutical Company has partially responded to a DPP-issued Pediatric Written Request (PWR) for studies of aripiprazole for the short-term treatment of schizophrenia and the acute manic episodes of Bipolar I Disorder in the pediatric population.

The PWR for studying both indications (schizophrenia in adolescents and Bipolar I Disorder in children and adolescents) was issued on February 11, 2003. The main requirements were to conduct a pediatric PK study, efficacy studies in pediatric schizophrenia and Bipolar I Disorder, and a long-term pediatric safety study. The age groups for study were defined as adolescents (13-17 years old) for schizophrenia, and children and adolescents (10-17 years old) for Bipolar I Disorder.

The Division met with the sponsor multiple times to discuss the requirements of the PWR and to provide input on study protocols. Although both indications of schizophrenia and Bipolar I Disorder are required by the PWR, Otsuka elected to submit the data for each indication in separate efficacy supplements. The pediatric Bipolar I Disorder efficacy supplement was only recently received, but the sponsor has submitted the PK study, short-term schizophrenia safety and efficacy study, and a sufficient amount of long-term safety data in pediatric patients to make a determination on this pediatric schizophrenia sNDA and this memo will focus on those data.

This sNDA has been reviewed by Jing Zhang, M.D., Medical Officer, DPP, Yeh-Fong Chen, Ph.D., Office of Biostatistics, and Andre Jackson, Ph.D., Office of Clinical Pharmacology. There are no new animal pharmacology/toxicology data to review as part of this submission. Aripiprazole is an approved drug with no new CMC or toxicology data required for this submission, and it was

determined that an Environmental Assessment was not required. This is the first presentation of the ABILIFY label in the new PLR format.

2 CLINICAL PHARMACOLOGY

The Clinical Pharmacologists have evaluated the PK study submitted in response to the PWR (repeated doses of aripiprazole administered to pediatric patients with schizophrenia or bipolar spectrum disorders) and have determined that AUC and Cmax appear to be linear in the pediatric population and so rational decisions can be made about dosing. They have reviewed and suggested changes relevant to clinical pharmacology for the newly added pediatric schizophrenia sections of the sponsor's proposed labeling.

3 CLINICAL DATA

Overview of Studies

In response to the Agency-issued PWR, Otsuka developed the aripiprazole pediatric efficacy program (APEX) which consists of four studies: one safety/tolerability/PK study (31-03-238), two short-term, randomized, double-blind, placebo-controlled safety and efficacy studies—one each in schizophrenia (31-03-239) and bipolar mania (31-03-240), and an open-label continuation safety study (31-03-241) enrolling patients who complete either of the short-term studies. To date the review team has considered all but the recently submitted study in pediatric bipolar disorder, which is the subject of a separate sNDA.

Efficacy Findings

Study 31-3-239 was a randomized, double-blind, placebo-controlled, multi-center study conducted in approximately 300 adolescent subjects (13 – 17 years of age) diagnosed with schizophrenia at 141 sites in 13 countries including the United States. It included 3 treatment groups: placebo, aripiprazole 10 mg/day, and aripiprazole 30 mg/day. The diagnosis of schizophrenia was confirmed by a valid and reliable semi-structured interview (K-SADS-PL) as required by the PWR. After a screening/washout phase and appropriate dose escalation period (5 days for the 10 mg/day group and 11 days for the 30 mg/day group) to the target fixed dose, pediatric patients with schizophrenia were entered into a six week double-blind treatment phase. Eligible patients who completed this study were then offered enrollment into the open-label safety study for an additional 6 months of treatment.

The primary efficacy measure was the mean change from baseline to endpoint (Day 42) in the Positive and Negative Symptom Scale for Schizophrenia (PANSS) total score. Multiple secondary endpoints were specified (none as key secondary endpoints) and included mean changes from baseline to endpoint (Day 42) in the Children's Global Assessment Scale—CGAS, CGI-Severity scale, CGI-Improvement scale, and PANSS Positive and Negative Symptom subscales. Comparison of the mean changes in primary or secondary endpoints between doses of aripiprazole was not specified as a secondary endpoint. Last observations were carried forward to week 6. The results are shown in the table below.

Study 31-03-239: Mean Change from Baseline PANSS Total Score by Week (LOCF)

Visit/Week	Arip 10 mg		Arip 30 mg		Placebo		P-value Arip10 mg vs. Placebo	P-value Arip 30 mg vs. Placebo
	N	Mean*	N	Mean*	N	Mean*		
Baseline	99	93.7	97	94.9	98	95.0	0.5375	0.9372
Week 1	98	-6.9	95	-10.4	97	-7.2	0.8390	0.0465
Week 2	99	-13.9	97	-15.2	98	-12.5	0.4748	0.1828
Week 3	99	-18.4	97	-22.1	98	-16.7	0.4759	0.0269
Week 4	99	-21.8	97	-24.6	98	-19.0	0.2346	0.0181
Week 5	99	-24.5	97	-27.3	98	-20.3	0.0979	0.0057
Week 6	99	-26.7	97	-28.6	98	-21.2	0.0414	0.0061

* The reported means are least square means adjusted from an ANCOVA model of change from baseline, with baseline as a covariate and terms for treatment and region strata.

Dr. Chen confirmed the sponsor's analysis methods and results for the primary and secondary endpoints and agreed that aripiprazole demonstrated efficacy at both 10 mg/day and 30 mg/day in pediatric patients with schizophrenia. She determined that the difference in mean change PANSS scores at endpoint between aripiprazole dosing groups was not statistically significant. Dr. Zhang points out that 30 mg/day is minimally numerically superior to 10 mg/day (b) (4) I agree with the review team: aripiprazole is effective in the pediatric schizophrenia population (b) (4)

Baseline disease severity and concomitant medication use were determined to by similar among study groups. Subgroup analyses for region, gender, and race demonstrated no convincing differences in response based upon subgroups.

Efficacy Conclusions

It is clear from the data presented above that aripiprazole is effective in treating pediatric schizophrenia. Drs. Zhang and Chen have noted in their reviews that both doses (10 mg/day and 30 mg/day) have similar efficacy. This is not say that some patients would not benefit from a dose higher than 10 mg/day, but there was not a statistically evident increase in response to the higher dose. We will note this information in labeling so that prescribers may use the clinical trial data to help make dosing decisions.

Safety Data

Treatment of pediatric patients with aripiprazole has been reasonably safe and well tolerated. The safety profile for use in pediatric patients appears similar to that in adults excepting for some increased somnolence, EPS, and tremor.

Studies Used to Assess Safety

The safety review of aripiprazole is based on data from Study 31-03-239 (short-term safety/efficacy study) and Study 31-03-241 (open-label 6 month study). As explained above, safety information from the PWR-required study in pediatric Bipolar I Disorder was not reviewed as part of this sNDA.

A total of 202 patients were exposed to aripiprazole in Study 31-03-239 (100 at 10 mg/day, 102 at 30 mg/day). Approximately 1/3 of these patients continued beyond the scheduled 42 days of

treatment as part of the long-term safety study. As of 9 Nov 2006 (the cut-off date for data submission), there were 119 patient-years of pediatric exposure with an average aripiprazole dose of 16.1 mg/day.

Deaths

There were no deaths in the short-term trial. One death did occur in the long-term open-label study, but it was unrelated to study drug (accidental electrocution).

Serious Adverse Events (SAEs)

Approximately 4% of aripiprazole-treated patients and 3% of placebo-treated patients experienced SAEs during Study 31-03-241, but the only SAE likely related to drug was extrapyramidal disorder (see the table below for details).

Study 31-03-239: All Serious Treatment-emergent Adverse Events

Class and MedDRA Preferred Term	Aripiprazole 10 mg (N = 100) n (%)	Aripiprazole 30 mg (N = 102) n (%)	Placebo (N = 100) n (%)	Total (N = 302) n (%)
Total subjects with at least one SAE	4 (4.0)	4 (3.9)	3 (3.0)	11 (3.6)
Infections and Infestations				
Varicella	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.3)
Injury, Poisoning, and Procedural Complications				
Intentional overdose	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.3)
Overdose	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.3)
Nervous System Disorders				
Extrapyramidal disorder	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.3)
Neuroleptic malignant syndrome [a]	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.3)
Psychiatric Disorders				
Aggression	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.3)
Depression	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.3)
Psychotic disorder	1 (1.0)	1 (1.0)	1 (1.0)	3 (1.0)
Schizophrenia	1 (1.0)	1 (1.0)	0 (0.0)	2 (0.7)
Suicidal ideation	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.3)
Suicide attempt	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.3)
Vascular Disorders				
Thrombophlebitis	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.3)

Adverse Events Leading to Dropout

The profile of dropouts from the controlled trial is summarized in the table below. The most common reasons for discontinuation from the study were withdrawal of consent and AEs. The treatment-emergent AEs which were most likely related to drug include nausea, dystonia, and somnolence.

Treatment-emergent and dose-related EPS was seen in the controlled trial (see table below). As has been observed in other atypical antipsychotic trials in the pediatric population, EPS occurred at a higher frequency than in adults, and is dose-related.

Study 31-03-239: Treatment-emergent AEs related to EPS Symptoms

Class and MedDRA Preferred Term	Aripiprazole 10 mg (N = 100) n (%)	Aripiprazole 30 mg (N = 102) n (%)	Placebo (N = 100) n (%)	Total (N = 302) n (%)
Gastrointestinal Disorders				
Salivary hypersecretion	1 (1.0)	3 (2.9)	1 (1.0)	5 (1.7)
General Disorders and Administration Site Conditions				
Gait disturbance	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.3)
Musculoskeletal and Connective Tissue Disorders				
Joint stiffness	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.3)
Muscle rigidity	1 (1.0)	1 (1.0)	0 (0.0)	2 (0.7)
Nervous System Disorders				
Akathisia	5 (5.0)	12 (11.8)	5 (5.0)	22 (7.3)
Drooling	0 (0.0)	3 (2.9)	0 (0.0)	3 (1.0)
Dyskinesia	1 (1.0)	2 (2.0)	0 (0.0)	3 (1.0)
Dystonia	3 (3.0)	1 (1.0)	0 (0.0)	4 (1.3)
Extrapyramidal disorder	13 (13.0)	22 (21.6)	5 (5.0)	40 (13.2)
Hyperkinesia	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.3)
Myoclonus	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.3)
Neuroleptic malignant syndrome[a]	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.3)
Tremor	2 (2.0)	12 (11.8)	2 (2.0)	16 (5.3)

Common and Drug-Related Adverse Events

The majority of treatment-emergent adverse events (TEAEs) were mild to moderate in severity. TEAEs classified as severe actually occurred more frequently in the 10 mg/day group (7%) than the 30 mg/day group (3.9%), which was only slightly higher than in the placebo group (3.0%). Potentially drug-related TEAEs included akathisia, extrapyramidal disorder, somnolence, and tremor (see table below).

Study 31-03-239: Commonly (>5% in Any Treatment Group) Reported TEAEs

Class and MedDRA Preferred Term	Aripiprazole 10 mg (N = 100) n (%)	Aripiprazole 30 mg (N = 102) n (%)	Placebo (N = 100) n (%)	Total (N = 302) n (%)
Total subjects with at least one TEAE	71 (71.0)	74 (72.5)	57 (57.0)	202 (66.9)
Gastrointestinal Disorders				
Nausea	9 (9.0)	10 (9.8)	6 (6.0)	25 (8.3)
Vomiting	5 (5.0)	3 (2.9)	5 (5.0)	13 (4.3)
Infections and Infestations				
Nasopharyngitis	5 (5.0)	5 (4.9)	4 (4.0)	14 (4.6)
Nervous System Disorders				
Akathisia	5 (5.0)	12 (11.8)	5 (5.0)	22 (7.3)
Dizziness	7 (7.0)	4 (3.9)	3 (3.0)	14 (4.6)
Extrapyramidal disorder	13 (13.0)	22 (21.6)	5 (5.0)	40 (13.2)
Headache	16 (16.0)	11 (10.8)	10 (10.0)	37 (12.3)
Somnolence	11 (11.0)	22 (21.6)	6 (6.0)	39 (12.9)
Tremor	2 (2.0)	12 (11.8)	2 (2.0)	16 (5.3)
Psychiatric Disorders				
Agitation	1 (1.0)	3 (2.9)	5 (5.0)	9 (3.0)
Insomnia	11 (11.0)	10 (9.8)	15 (15.0)	36 (11.9)

Vital Sign Changes

No clinically relevant mean changes in vital sign parameters were noted between treatment groups and placebo. No treatment-emergent vital sign abnormalities were classified as serious or resulted in discontinuation from the short-term trial.

ECG Findings

No clinically meaningful trends were observed for any of the potentially clinically significant changes seen in ECG parameters. QT interval analysis revealed a small decrease in QTc in the aripiprazole arms compared to placebo. This decrease was not determined to be clinically significant (< 7 msec) by Dr. Zhang in consultation with the QT team in the Division of Cardio-Renal Drug Products.

Changes in Body Weight

In both the controlled short-term trial and the open-label long-term safety study, mean changes from baseline for body weight and BMI z-scores were within ½ a standard deviation of the general population for all treatment arms. This minimal effect on body weight and BMI were observed for both male and female patients.

Laboratory Findings

No clinically relevant mean changes were noted in serum chemistries, hematology parameters, serum insulin concentration, or urinalysis. A small mean decrease in serum prolactin (relative to baseline) was observed, but the majority of these patients had very recently been exposed to other antipsychotics prior to entering this study, and this previous exposure may have elevated prolactin

prior to their entering the double-blind phase of the current study. The small mean changes observed in serum prolactin appear to have no clinical relevance. No SAEs or discontinuations were related to laboratory abnormalities.

Metabolic Syndrome Evaluation
Dr. Zhang found no clinically meaningful changes from baseline in mean values for fasting serum tryiglycerides, fasting serum HDL, fasting serum glucose, waist circumference, or BMI.

Literature Review
The sponsor conducted and Dr. Zhang reviewed the world literature on use of aripiprazole in the pediatric population. There were no findings that would alter the conclusions of this review.

Conclusion Regarding Safety
Short-term treatment of pediatric patients diagnosed with schizophrenia with aripiprazole appears to have been reasonably safe and there were no unexpected adverse events. Aripiprazole exhibits a very similar safety profile in adults and in pediatric patients with the exception of dose-related somnolence, tremor, and EPS, which occur at a greater frequency in pediatric patients taking the drug.

PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING
This NDA was not presented to the PDAC.

8.0 DSI INSPECTIONS
Two sites study sites were inspected (San Juan, Puerto Rico and Varna, Bulgaria) with a final classification of VAI-No response requested; data acceptable.

9.0 LABELING AND ACTION LETTER

9.1 Final Draft of Labeling Attached to the Action Package
The sponsor's proposed labeling is presented in the new PLR format and will require some modification as described throughout this review. We will negotiate our changes and attach labeling to the Action Letter.

9.2 DMETS
Abilify™ is an approved trade name.

10.0 PHASE 4 COMMITMENTS
No Phase 4 requirements have been identified.

11.0 CONCLUSION AND RECOMMENDATION
The sponsor has submitted sufficient data to support that aripiprazole is effective and reasonably safe in the treatment of pediatric schizophrenia, and we should proceed with an APPROVAL action. A determination on pediatric exclusivity will be made after the data submitted in support of the sNDA for pediatric Bipolar I Disorder are reviewed for compliance with the terms of the PWR.

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/s/

Mitchell Mathis
9/14/2007 01:49:58 PM
MEDICAL OFFICER
AP Rec

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-436/S017

21-713/S012

21-729/S004

21-866/S004

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA 21436-017 NDA 21713-012 NDA 21729-004 NDA 21866-004
Submission Number	017
Submission Code	SE5
Letter Date	March 23, 2007
Stamp Date	March 24, 2007
PDUFA Goal Date	September 26, 2007
Reviewer Name	Jing Zhang, MD, PhD
Review Completion Date	August 22, 2007
Established Name	Aripiprazole
(Proposed) Trade Name	Abilify®
Therapeutic Class	Atypical Antipsychotics
Applicant	Otsuka Pharmaceutical Company
Priority Designation	P
Formulation	2, 5, 10 and 15 mg oral tablets
Dosing Regimen	10 mg (b) (4)
Indication	Schizophrenia
Intended Population	Children/Adolescents

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Based on the data available at the time of completion of this review, I recommend that this supplement NDA be granted approvable status.

I recommend a few labeling changes. Details can be found in section 9.4 Labeling Review.

(b) (4)

Final approval is contingent on mutual agreement on labeling (b) (4) .

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

There are no additional recommendations for risk management activity.

1.2.2 Required Phase 4 Commitments

No Phase 4 commitments are required at this time point.

1.2.3 Other Phase 4 Requests

There are no other Phase 4 requests.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

In response to the FDA's Pediatric Written Request (PWR) dated February 11, 2003, the sponsor designed the aripiprazole pediatric efficacy program (APEX) to provide controlled clinical data regarding the use of aripiprazole for the treatment of schizophrenia in the adolescent population and mania associated with bipolar disorder in the child and adolescent population. The APEX program included four studies: one safety, tolerability and pharmacokinetic (PK) study (31-03-238), two randomized, double-blind, placebo-controlled safety and efficacy study—one for

schizophrenia (31-03-239) and one for bipolar mania (31-03-240), and a roll-over, open-label long-term safety study (31-03-241) for subjects who complete either of the double-blind trials.

This submission includes data from 2 completed studies—Study 31-03-238 (PK study) and Study 31-03-239 (acute controlled study for adolescent schizophrenia) and one ongoing study—Study 31-03-241(long-term safety study). From this submission, the sponsor intended to seek for approval of the acute (b) (4) treatment indication for pediatric schizophrenia.

Study 31-03-238 is a child and adolescent PK study designed to assess the safety, tolerability and PK of repeating doses of aripiprazole following oral administration in children (10 to 17 years) with a primary diagnosis of schizophrenia or bipolar disorder. This PK study is reviewed by Andre J. Jackson, PhD, a Bio-Pharm reviewer from OTC/DCRI. At the time of completion of this review, Dr. Jackson's review is still pending.

Study 31-03-239 is a 6-week, multicenter, randomized, double-blind, placebo-controlled study to assess the efficacy and safety of oral aripiprazole at doses 10 mg/d and 30 mg/d in adolescents (13 to 17 years) with primary diagnosis of schizophrenia. The data from this study including both efficacy and safety data were reviewed in detail in this review.

Study 31-03-241 is an ongoing, 6-month, multicenter, open-label, flexible-dose (2 to 30 mg/d) safety and tolerability study in children and adolescent with primary diagnosis of schizophrenia and bipolar disorder to provide additional long-term safety and tolerability data for oral aripiprazole. The clinical data cut-off date for inclusion of data for this submission was 09 Nov. 2006. The safety data from this study were used to detect deaths and unexpected serious adverse events associated with long-term oral aripiprazole treatment. Aripiprazole's long-term effects on children's growth (waist circumference, BMI, weight, and z-scores) were also reviewed. Because there was no control arm in this study, the value of these data is limited.

The primary components of this supplement NDA are as follows:

- Clinical study report (CSR) for 31-03-238 (PWR required Pharmacokinetic study in the pediatric Schizophrenia and Bipolar Mania population)
- CSR for 31-03-239 (PWR required controlled efficacy and safety study in Adolescent Schizophrenia population)
- Combined Long-term Safety Synopsis for 31-03-239 and the open-label, long-term safety study in pediatric Schizophrenia and Bipolar Mania population, 31-03-241
- Revised Abilify labeling in Physician's Labeling Rule (PLR) format

1.3.2 Efficacy

The efficacy of aripiprazole in the acute schizophrenia treatment in pediatric population was demonstrated by efficacy data from Study 31-03-239. Aripiprazole was effective in the treatment of pediatric schizophrenia at daily doses of 10 mg and 30 mg, as demonstrated by statistically significant improvements compared to placebo in PANSS total score at Week 6.

1.3.3 Safety

This safety review is based on safety data from Study 31-03-239 and 31-03-241. The safety findings from this submission were consistent with the previously observed aripiprazole safety profile. No any unexpected serious adverse events (SAEs) or deaths associated with aripiprazole treatment were reported.

1.3.4 Dosing Regimen and Administration

Study 31-03-239 is a fixed-dose study. Patients who met the inclusion criteria were randomized into one of following treatment arms: aripiprazole 10 mg, aripiprazole 30 mg or placebo. All study drugs were administered orally for 6 weeks. A one-time dose reduction to 5 mg/day in the 10 mg treatment arm and to 15 mg/day in the 30 mg treatment arm after Day 25 for dose-related tolerability issues was permitted.

Study 31-03-241 is a flexible-dose, open-label study. The dose range was aripiprazole 2 to 30 mg/d administered orally for 6 months.

1.3.5 Drug-Drug Interactions

The existing aripiprazole label addresses safety outcome related to potential drug-drug interactions. There have been no new data generated on this topic from this submission.

1.3.6 Special Populations

All three studies submitted to this submission are pediatric studies. There are no new data generated on other special populations from this submission.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Aripiprazole is a dopamine presynaptic D_2 auto-receptor partial agonist and belongs to atypical antipsychotic family. Same as other atypical antipsychotics, aripiprazole also acts as an antagonist at serotonin 5-HT_{1A} receptor.

Abilify® (aripiprazole, OPC-14597, BMS-337039) is approved in the United States for the treatment of adults with acute schizophrenia (as of November 2002), maintenance of stability in schizophrenia (as of August 2003), treatment of acute manic and mixed episodes associated bipolar disorder (as of September 2004), and for the maintenance of efficacy in bipolar I disorder (as of March 2005). Aripiprazole is also approved for the treatment of schizophrenia in the European Union, Australia, and a number of countries in Asia, Europe, and Latin America. The safety of aripiprazole tablets has been studied in approximately 8456 adult subjects to date. There is a general lack of clinical research in pediatric and adolescent subjects having schizophrenia.

2.2 Currently Available Treatment for Indications

Risperidone is the only antipsychotic that has been approved by FDA for the indication of pediatric schizophrenia (Aug. 2007). However, other antipsychotics, especially atypical antipsychotics, have been widely used off-label in real clinical practice for this indication.

2.3 Availability of Proposed Active Ingredient in the United States

Aripiprazole is an approved drug in the United Sates.

2.4 Important Issues With Pharmacologically Related Products

Aripiprazole is the only FDA approved atypical antipsychotic with dopamine D_2 receptor partial agonist property. As a member of atypical antipsychotics, aripiprazole labeling carries same class warnings and precautions as other atypical antipsychotics. No important issues with pharmacologically related products were identified from this submission.

2.5 Presubmission Regulatory Activity

Feb. 11, 2003 Pediatric Written Request (PWR) for pediatric studies in schizophrenia and bipolar mania was issued by FDA to Otsuka.

Nov. 13, 2003 Otsuka met with FDA to discuss Abilify Pediatric Exclusivity Program.

April 7, 2004 New protocol for Study 31-03-238 (adolescent PK study) was submitted to FDA.

June 8, 2004 A telecon was held on June 8th 2004 to discuss clarifications and proposals from Otsuka regarding FDA's PWR for Abilify.

July 1, 2004 New protocol for Study 31-03-239 (adolescent schizophrenia study) was submitted to FDA.

Aug. 6, 2004 New protocol for Study 31-03-241 (adolescent bipolar mania study) was submitted to FDA.

Dec. 13, 2006 Otsuka submitted IND 42,776 for the adolescent schizophrenia indication.

Jan. 18, 2007 Pre-NDA meeting with FDA discussed results of adolescent schizophrenia trial done in response to PWR and discussed possible sNDA submission seeking an indication in adolescent population.

Mar. 23, 2007 Otsuka submitted this sNDA for Ability in the treatment of adolescent schizophrenia.

(b) (4)

2.6 Other Relevant Background Information

Abilify (aripiprazole) is approved for the treatment of acute schizophrenia, maintenance of stability in schizophrenia, treatment of acute manic episodes associated with Bipolar I Disorder and for the maintenance of efficacy in Bipolar I Disorder, in the United States. It is also being evaluated for (b) (4) in a collaborative program between Marketing Holder Authorization Otsuka Pharmaceutical Company (OPC) and co-marketer Bristol-Myers Squibb Company (BMS). Besides US, Aripiprazole is marketed for the treatment of schizophrenia in Mexico, Brazil, Puerto Rico, Australia, Korea, Peru, Germany, U.K., Columbia, Chile, Ireland, Switzerland, Sweden, Denmark, Greece, Venezuela, Finland, Iceland, Netherlands and Singapore. Aripiprazole is also approved for the treatment of schizophrenia in Taiwan, Indonesia, France, Spain, Italy, Belgium, Luxembourg, Austria, Hungary, Portugal, Slovakia, Czech Republic, Latvia, Estonia, Poland, Norway, Aruba, Ecuador, Trinidad & Tobago, and Curacao.

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

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Aripiprazole is a FDA approved drug. No new CMC data were submitted to this sNDA. Environmental assessment was not deemed necessary at this time point.

3.2 Animal Pharmacology/Toxicology

There is no animal pharmacology/toxicology data provided in this submission. These studies were not deemed necessary.

3.3 Statistical Review and Evaluation

Yeh-Fong Chen, PhD., is the statistical reviewer for this sNDA. In her review, she confirmed the sponsor's analysis results for the primary and secondary endpoints for Study 31-03-239 and agreed with the conclusion that aripiprazole is effective at doses of 10 mg/d (b) (4)

(b) (4)

3.4 Bio-Pharmacology Review and Evaluation

Andre J. Jackson, PhD, is the Bio-Pharm reviewer for this submission. At the time of completion of this review, Dr. Jackson's review is still pending.

3.5 Clinical Sites Inspection

Two study sites were selected for inspection by the Division of Scientific Inspection because of relatively larger enrollment in Study 31-03-239. Dr. Michel Woodbury Fariña (Site 074) and Dr. Stefan Todorov (Site 104) are principle investigators in these two sites. The inspections were conducted from Aug. 7, 2007 to Aug. 16, 2007. The inspector found a few minor deficiencies of data at each study site. However, the inspector felt the deficiencies were unlikely to have an effect on data reliability and she concluded that data from these two investigators are acceptable.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

Efficacy data to support the efficacy claims in this submission are from Clinical Study Report for Study 31-03-239.

Safety data to support the safety conclusions in pediatric schizophrenia population are from Clinical Study Report for Study 31-03-239 and Combined Long-term Safety Synopsis for 31-03-239 and Study 31-03-241.

4.2 Tables of Clinical Studies

Table 1 summarizes studies included in the efficacy and safety review for this submission.

Table 1 Clinical Studies Included in Efficacy and Safety Review

Protocol No. Study Design	Study Objective	Duration	Dose, and Regimen
31-03-239 A multicenter, randomized, double-blind, placebo controlled and fixed-dose study in treatment of adolescents with primary diagnosis of schizophrenia.	To assess the short-term safety, and efficacy of oral aripiprazole at doses of 10 mg/d and 30 mg/d in adolescents (10 to 17 years).	6 weeks	Arip 10 mg po qd Arip 30 mg po qd Placebo po qd
31-03-241 A multicenter, open-label and flexible-dose study in patients who completed Study 31-03-239 or had withdrawn from the double-blind extension phase of Study 31-03-240.	To assess the long-term safety and tolerability of flexible-dose aripiprazole in adolescent patients with diagnosis of schizophrenia.	6 months	2 to 30 mg po qd

4.3 Review Strategy

A list of the items examined during the course of this review is provided in Table 2.

Table 2 Items Utilized in the Review

Submission Date	Submission Type	Items Reviewed
March 23, 2007	Initial sNDA	CSR for Study 31-03-239 Synopsis CSR for combined analysis of Study 31-03-239 and 31-03-241 Case report tablulations (.xpt files) Case report forms
May 22, 2007	Amendment	Additional CRFs A completed literature search for Abilify
June 6, 2007	Amendment	A completed table of information in response to the PWR requirements
June 21, 2007	Amendment	Additional financial disclosure information
(b) (4)		

4.4 Data Quality and Integrity

Case Report Forms, Narrative Summaries, and adverse events (.xpt file), as well as AE coding (compared investigator's verbatim terms with MedDRA preferred terms) were examined for consistency of adverse event information across documents and acceptability of AE coding. No significant inconsistency was found.

Two study sites (Site 074 and 104) in Study 31-03-239 were selected for scientific inspection by DSI. Minor deficiencies of data were found at each study site. However, the inspector felt that the deficiencies were unlikely to have an effect on data reliability.

4.5 Compliance with Good Clinical Practices

All studies were performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with ICH/Good Clinical Practice and applicable regulatory requirements.

4.6 Financial Disclosures

As of March 8, 2007 the sponsor received a total of 143 of the 143 financial disclosures for investigators. Two sites had a change in principal investigator during the course of the study, resulting in a total of 143 investigator financial disclosures for 141 sites. One investigator had financial interest information to disclose. The sponsor received 583 of the 593 disclosure forms from sub-investigators. None of the sub-investigators had financial interest information to disclose. There are a total of 10 forms that have not been received to date from sub-investigators.

(b) (6) received $2,500.00 on (b) (6), and he also received $2,500 on (b) (6). Since his site contributed (6) patients (b) (6), the financial payment (b) (6) received unlikely biased the study results.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Andre J. Jackson, PhD., is the primary Bio-Pharm reviewer. Details can be found in Dr. Jackson's review.

5.2 Pharmacodynamics

Andre J. Jackson, PhD., is the primary Bio-Pharm reviewer. Details can be found in Dr. Jackson's review.

5.3 Exposure-Response Relationships

Exposure-response relationship was not particularly studied in these studies. In Study 31-03-239, aripiprazole 30 mg arm didn't demonstrate significant superiority to aripiprazole 10 mg arm in mean change from baseline in PANSS Total Score (arip 10 mg vs 30 mg: -26.6 vis -28.6).

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

In the original submission, Otsuka proposed the acute treatment indication for pediatric schizophrenia. (b) (4)

6.1.1 Methods

The clinical study report for Study 31-03-239 is the main data source for this efficacy review (b) (4). Data from Study 31-03-241 were mainly reviewed in safety review section. The efficacy review was performed in consultation with the statistical reviewer, Yeh-Fong Chen, PhD.

6.1.2 General Discussion of Endpoints

Positive and Negative Syndrome Scale (PANSS) is the primary endpoint in Study 31-03-239. PANSS is one of most commonly used instruments for measuring symptom reduction of schizophrenia patients in the antipsychotic therapy trials. PANSS is a 30-item rating instrument evaluating the presence/absence and severity of positive, negative and general psychopathology of schizophrenia. Use of the PANSS as a tool for assessing the efficacy of treatments for schizophrenia and other psychotic disorders in studies in pediatric and adolescent patients is well documented. The scale was developed from the Brief Psychiatric Rating Scale (BPRS) and the Psychopathology Rating Scale. All 30 items are rated on a 7-point scale (1=absent, 7=extreme). Compare to BPRS, PANSS addresses broader psychopathology and has greater reliability. However, challenges of the PANSS are difficulties to conduct patient interview (30-40 min.) and patient subjectiveness (items are assessed based on patient perceptions).

Primary Endpoint:
Mean change from baseline to endpoint in the PANSS total score

Secondary Endpoint:

- Mean change from baseline to endpoint in the children's Global Assessment Scale (CGAS)
- Mean change from baseline to endpoint in the Clinical Global Impression Severity (CGI-S) Scale and CGI-Improvement Scale
- Mean change from baseline to endpoint in the PANSS Positive and Negative Subscales
- Time to discontinuation due to all reasons

6.1.3 Study Design

6.1.3.1 Investigators/Sites

Study 31-03-239 was conducted in Argentina, Bulgaria, Croatia, India, Jamaica, Mexico, Romania, Russia, Serbia, South Africa, South Korea, Ukraine, and the US in approximately 300 subjects at 141 study centers. The principal investigators, study centers, and number of subjects screened and enrolled per center are listed in Appendices 10.1.

6.1.3.2 Objectives

The primary objective of the study is to determine the safety and efficacy of aripiprazole tablets at doses of 10 mg/day and 30 mg/day in adolescent patients, ages 13-17 years, with primary diagnosis of schizophrenia.

6.1.3.3 Subjects

Key Inclusion Criteria:

- Male and Female patients aged 13 to 17 with a K-SADS-PL confirmed DSM-IV diagnosis of schizophrenia. Schizophrenia must be the primary DSM-IV axis I diagnosis.
- Patients who have a PANSS score ≥ 70 at baseline.

Exclusion Criteria:

- Patients with an Axis I diagnosis of schizoaffective disorder, or a current diagnosis of major depressive episode.
- Patients presenting with a clinical picture and/or history that is consistent with delirium, amnestic or other cognitive disorder, or bipolar disorder; Subjects with psychotic symptoms that are better accounted for by another general medical condition or direct psychological effect of a substance (i.e., medication).
- Patients hospitalized within 14 days prior to screening visit for current acute episode of schizophrenia.
- Patients with known mental retardation.
- Patients with childbearing potential, who are not practicing double-barrier birth control, or, who will not remain abstinent during the study, and for 30 days (for females) and for 90 days (for males) following the last dose of study medication.
- Females who are breast-feeding and/or who have a positive urine and/or serum pregnancy test result, prior to receiving study drug.
- The patient had been previously involved in a clinical study with aripiprazole or is currently treated with aripiprazole.
- The patient has a known allergy or hypersensitivity to aripiprazole or other quinolinones.
- The patient is considered treatment resistant to antipsychotic medication, in the opinion of the investigator, based on prior trials of two different antipsychotics that were of adequate dose and duration.
- The patient has a history of neuroleptic malignant syndrome.
- The patient represents a significant risk of committing suicide, or with a score > 3 on the Suicidal Ideation item of the Children's Depression Rating Scale-Revised (CDRS-R).
- The patient has met DSM-IV criteria for substance or alcohol abuse or dependence within the past 3 months with the exception of abuse of marijuana.
- A positive drug screen for substance use (excluding marijuana).
- The patients have clinically significant medical conditions.
- The patient has participated in any clinical trial with an investigational product within the past month.

6.1.3.4 Overall Study Design

This is a multicenter, randomized, double-blind, placebo-controlled study designed to assess the safety and efficacy of two fixed doses of aripiprazole (10 mg and 30 mg) compared to placebo in adolescent patients, ages 13 to 17 years, with a DSM-IV diagnosis of schizophrenia.

The study consists of three arms. After a minimum of a 3-day antipsychotic washout period, subjects were randomized to either 10 mg or 30 mg of aripiprazole, or to placebo. All study medications were administered orally. Aripiprazole was titrated to the target dose in 5 days in the

10 mg treatment arm, and in 11 days in the 30 mg treatment arm. Patients remained at the assigned fixed dose for at least two weeks. Patients who experienced dose-related tolerability issue prior to study Day 25, were discontinued from the study. After study Day 25, investigators were able to decrease the dose of aripiprazole for tolerability to 5 mg/day in the 10 mg treatment arm and to 15 mg/day in the 30 mg treatment arm.

This 42 days (6-week) study was conducted either on an outpatient basis or in a partial or full inpatient basis at any given time of the study. Mandatory patient evaluations took place at Days 1 (Baseline), (phone call on Day 4), 7, 14, 21, 28, 35, and 42. Eligible patients who completed the 42-day study had the option to enroll into an open-label safety trial of aripiprazole (protocol number: 31-03-241) for an additional six months.

Any mood-stabilizing medications, antidepressants, or psychotropics must have been discontinued at least 3 days (fluoxetine for 4 weeks) prior to administration of study drug (or placebo). Stimulants or other ADHD medications (e.g., atomoxetine) must have been discontinued for 5 halflives prior to receiving the first dose of study drug (or placebo).

During the course of study, if the primary efficacy endpoint is unchanged or worsened, or if deemed absolutely necessary by the treating physician, patients might receive benzodiazepine or anticholinergics for clinical indications other than prophylactic use. Treatment with benzodiazepines within 4 hours prior to rating scale administration, or treatment with anticholinergic agents within 12 hours prior to rating scale administration was prohibited.

6.1.3.5 Statistical Analysis Plan

The core dataset for all efficacy analyses is the Intent-to-Treat (ITT) dataset which consist of data from all randomized subjects. In order to assess sensitivity of results due to missing data, two types of analyses—the LOCF and the OC are performed at a given visit. In order to understand time trends in efficacy, both the LOCF and AC analyses are performed at each visit.

Demographic characteristics, disease severity and medical history at (pre-dose) baseline were summarized by descriptive statistics, e.g., proportion, mean, median, standard deviation, minimum and maximum values. These summary statistics were reviewed to identify any potential lack of balance between the treatment groups.

The primary efficacy variable in this study is the change from baseline in PANSS Total Score. The primary statistical comparisons of interest are (a) aripiprazole 10 mg target dose vs. placebo, and (b) aripiprazole 30 mg target dose vs. placebo. Statistical analysis are performed by fitting an Analysis of Covariance (ANCOVA) model to the PANSS change scores with right hand terms for treatment, regional strata, and baseline total score. The Least Squares Means (LSM) obtained from a type III analysis using SAS are used to estimate the treatment comparisons. A nominal overall significance level of 0.05 (two-tailed) is used in testing statistical significance of these two comparisons. However, in order to account for multiplicity in testing the two comparisons, the Hochberg's procedure is used. In particular, the following procedure is followed. If both p-values are less than 0.05 (two-tailed), then statistical significance is declared for both doses;

however, if the larger of the two p-values is greater than 0.05 then the smaller p-value would be compared with 0.025 (two-tailed) and the corresponding treatment comparison will be declared statistically significant if this p-value is less than 0.025.

6.1.4 Efficacy Findings

6.1.4.1 Subject Disposition

Overall subject disposition is summarized in Table 3. A total of 302 subjects were randomized and treated in this study: 100/302 (33.1%) in the aripiprazole 10 mg arm, 102/302 (33.8%) in the aripiprazole 30 mg arm, and 100/302 (33.1%) in the placebo arm. Of these, 93/302 (30.8%) were randomized in the US, 141/302 (46.7%) were randomized in Europe, and 68/302 (22.5%) were randomized in other regions. All randomized subjects were included in the efficacy and safety analyses.

Subjects who completed the Day 42 visit were defined as completers. A total of 258/302 (85.4%) subjects completed the study: 84/100 (84.0%) in the aripiprazole 10 mg arm, 84/102 (82.4%) in the aripiprazole 30 mg arm, and 90/100 (90.0%) in the placebo arm.

Overall, adverse events (AEs) and subject withdrawal of consent were the most common reasons for discontinuation. A total of 7/100 (7.0%), 4/102 (3.9%), and 2/100 (2.0%) subjects withdrew due to AEs in the aripiprazole 10 mg, 30 mg, and placebo arms, respectively.

Table 3 Subject Disposition

	Aripiprazole 10 mg N (%)	Aripiprazole 30 mg N (%)	Placebo N (%)	Total N (%)
Randomized	100 (100.0)	102 (100.0)	100 (100.0)	302 (100.0)
Completed	84 (84.0)	84 (82.4)	90 (90.0)	258 (85.4)
Discontinued	16 (16.0)	18 (17.6)	10 (10.0)	44 (14.6)
AEs	7 (7.0)	4 (3.9)	2 (2.0)	13 (4.3)
Lost to follow up	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.3)
Subject withdrew consent	4 (4.0)	12 (11.8)	5 (5.0)	21 (7.0)
Protocol deviation	0 (0.0)	1 (1.0)	1 (1.0)	2 (0.7)
Lack of efficacy*	5 (5.0)	1 (1.0)	1 (1.0)	7 (2.3)
Analyzed for safety[a]	100 (100.0)	102 (100.0)	100 (100.0)	302 (100.0)
Analyzed for efficacy[b]	100 (100.0)	102 (100.0)	100 (100.0)	302 (100.0)

*: Lack of efficacy was determined by the investigators.
a: Subjects who received at least one dose of study medication were included in the safety analyses.
b: Randomized subjects evaluated for at least one primary or secondary efficacy parameter were included in the efficacy analysis.

A summary of subject disposition by regions is provided in Table 4. The overall completion and discontinuation rate cross regions was similar. Europe had slightly higher completion rate (89.4%) compared to US (81.7%) or Other Region (82.4%), which is caused by very low discontinuation rate in placebo arm in Europe (0% vs. 19.4% in US and 18.2% in Other Region).

Table 4 Subject Disposition by Regions

	Aripiprazole 10 mg N (%)	Aripiprazole 30 mg N (%)	Placebo N (%)	Total N (%)
Randomized	100 (100.0)	102 (100.0)	100 (100.0)	302 (100.0)
US	31 (100.0)	31 (100.0)	31 (100.0)	93 (100.0)
Europe	47 ((100.0)	47 (100.0)	47 (100.0)	141 (100.0)
Other region	22 (100.0)	24 (100.0)	22 (100.0)	68 (100.0)
Completed	84 (84.0)	84 (82.4)	90 (90.0)	258 (85.4)
US	26 (83.9)	25 (80.6)	25 (80.6)	76 (81.7)
Europe	39 (83.0)	40 (85.1)	47 (100.0)	126 (89.4)
Other region	19 (86.4)	19 (79.2)	18 (81.8)	56 (82.4)
Discontinued	16 (16.0)	18 (17.6)	10 (10.0)	44 (14.6)
US	5 (16.1)	6 (19.4)	6 (19.4)	17 (18.3)
Europe	8 (17.0)	7 (14.9)	0 (0.0)	15 (10.6)
Other region	3 (13.6)	5 (20.8)	4 (18.2)	12 (17.6)

6.1.4.2 Demographic Characteristics

Demographic characteristics are summarized in Table 5. The three treatment arms were demographically similar. The majority of subjects were male (171/302, 56.6%), and Caucasian (180/302, 60.0%). The mean age was 15.5 years. Male and Caucasian population were slightly lower respectively in Aripiprazole 10 mg arm (45%, 54%) compare to Aripiprazole 30 mg (63.7%, 64.0%) or placebo (61%, 60%) arm. Black population was slightly higher (17%) in Aripiprazole 10 mg compare to Aripiprazole 30 mg (11%) or Placebo (6%).

Table 5 Demographic Characteristics - All Randomized Subjects

Characteristic		Aripiprazole 10 mg (N = 100)	Aripiprazole 30 mg (N = 102)	Placebo (N = 100)	Total (N = 302)
Age (years)	N	100	102	100	302
	Mean (SD)	15.6 (1.3)	15.4 (1.4)	15.4 (1.4)	15.5 (1.4)
BMI	N	100	102	100	302
	Mean (SD)	23.5 (6.0)	23.0 (4.9)	22.9 (5.3)	23.1 (5.4)
Gender	Male, n (%)	45 (45.0)	65 (63.7)	61 (61.0)	171 (56.6)
	Female, n (%)	55 (55.0)	37 (36.3)	39 (39.0)	131 (43.4)
Race	Caucasian, n (%)	54 (54.0)	62 (61.0)	64 (64.0)	180 (60.0)
	Black, n (%)	17 (17.0)	11 (11.0)	6 (6.0)	34 (11.0)
	Asian, n (%)	16 (16.0)	12 (12.0)	15 (15.0)	43 (14.0)
	Others, n (%)	13 (13.0)	17 (17.0)	15 (15.0)	45 (14.6)

6.1.4.3 Disease Characteristics

Baseline disease severity, as measured by PANSS Total Score, CDRS-R Suicidal Ideations Score, and treatment status for previous episodes, are presented in Table 6. Overall, the baseline disease severity was comparable across all treatment arms. The mean PANSS Total Score and

CDRS-R Suicidal Ideations Score was 94.1 and 1.3, respectively. A total of 223/302 (74.0%) subjects had received treatment for previous episodes.

Table 6 Baseline Disease Severity

Characteristic		Aripiprazole 10 mg (N = 100)	Aripiprazole 30 mg (N = 102)	Placebo (N = 100)	Total (N = 302)
PANSS Total Score	N Mean (SD)	100 93.6 (15.7)	102 94.0 (16.1)	100 94.6 (15.6)	302 94.1 (15.8)
CDRD-R Suicidal Ideation Score	N Mean (SD)	100 1.3 (0.6)	102 1.3 (0.6)	99 1.3 (0.5)	301 1.3 (0.6)
Treatment given for previous episodes	Yes, n (%)	75 (75.0)	75 (74.0)	73 (73.0)	223 (74.0)

6.1.4.4 Concomitant Medications

Concomitant medications received by the subjects during study therapy (≥ 3% incidence overall) are presented in Table 7. The most commonly used medications during the follow-up period (by ≥ 3% incidence overall) were trihexyphenidyl and lorazepam. The psycholeptic utilization rate was very similar cross all treatment arms. It is less likely that concomitant medication use in this study would affect the efficacy outcomes.

Table 7 Concomitant Medications Used Most Commonly (≥ 3%) During Study Treatment

Drug Class/Medication Generic Name[a]	**Aripiprazole 10 mg (N = 100) n (%)[b]**	**Aripiprazole 30 mg (N = 102) n (%)[b]**	**Placebo (N = 100) n (%)[b]**	**Total (N = 302) n (%)[b]**
Total Using One or More Medications	55 (55.0)	59 (57.8)	47 (47.0)	161 (53.3)
Analgesics				
cotylenol	3 (3.0)	3 (2.9)	3 (3.0)	9 (3.0)
paracetamol	4 (4.0)	5 (4.9)	1 (1.0)	10 (3.3)
Anti-Parkinson Drugs				
benzatropine mesilate	3 (3.0)	5 (4.9)	1 (1.0)	9 (3.0)
biperiden	2 (2.0)	7 (6.9)	0 (0.0)	9 (3.0)
trihexyphenidyl	7 (7.0)	11 (10.8)	1 (1.0)	19 (6.3)
Anti-inflammatory and antirheumatic products				
ibuprofen	2 (2.0)	4 (3.9)	3 (3.0)	9 (3.0)
Psycholeptics				
clonazepam	3 (3.0)	4 (3.9)	3 (3.0)	10 (3.3)
diazepam	6 (6.0)	1 (1.0)	3 (3.0)	10 (3.3)
lorazepam	21 (21.0)	22 (21.6)	19 (19.0)	62 (20.5)
Vitamins	3 (3.0)	4 (3.9)	2 (2.0)	9 (3.0)

6.1.4.5 Efficacy Results

6.1.4.5.1 Primary Variable

The mean change from baseline to end point (6 weeks) in PANSS Total Score

The mean changes from baseline to end point in PANSS Total Score for the 10 mg and 30 mg aripiprazole arms versus placebo are presented in Table 8. Aripiprazole 10 mg and 30 mg showed statistically significant improvements over placebo in the PANSS Total Score at Week 6. Using the LOCF data set, the PANSS Total Scores at Week 6 were −26.7 in the aripiprazole 10 mg arm, −28.6 in the aripiprazole 30 mg arm, and −21.2 in the placebo arm. The comparison between aripiprazole and placebo was significant at both doses (p = 0.0414 for arip 10 mg vs placebo; p = 0.0061 for arip 30 mg vs placebo). The difference from placebo in mean change from baseline at Week 6 was −5.46 (95% CI = −10.7 to -0.21; p = 0.0414) for the aripiprazole 10 mg arm and −7.40 (95% CI = −12.7 to −2.13; p = 0.0061) for the aripiprazole 30 mg arm using LOCF dataset.

Table 8 Mean Change from Baseline to Endpoint in PANSS Total Score (LOCF)

	Aripiprazole 10 mg N = 99	Aripiprazole 30 mg N = 97	Placebo N = 98	P – value Aripiprazole vs Placebo	
				10 mg	30 mg
Baseline (LS Mean)	93.7	94.9	95.0		
Mean Change (LS Mean)	-26.7	-28.6	-21.2	0.0414	0.0061

The mean change from baseline in PANSS Total Score (LOCF) by visit is presented in Table 9. The aripiprazole 10 mg arm showed improvements over the placebo arm in the change from baseline in PANSS Total Score at all visits; however, the improvements were only statistically significant compared with placebo at Week 6. The aripiprazole 30 mg arm showed statistically significant improvements over placebo at Week 1, 3, 4, 5 and 6.

Table 9 Mean Change from Baseline to Endpoint in PANSS Total Score by Week (LOCF)

Visit/Week	Aripiprazole 10 mg N	Aripiprazole 10 mg LS Mean[a]	Aripiprazole 30 mg N	Aripiprazole 30 mg LS Mean[a]	Placebo N	Placebo LS Mean[a]	P-value[b] Aripiprazole 10 mg vs placebo	P-value[b] Aripiprazole 30 mg vs placebo
Baseline[c]	99	93.7	97	94.9	98	95.0	0.5375	0.9372
Week 1	98	-6.9	95	-10.4	97	-7.2	0.8390	0.0465
Week 2	99	-13.9	97	-15.2	98	-12.5	0.4748	0.1828
Week 3	99	-18.4	97	-22.1	98	-16.7	0.4759	0.0269
Week 4	99	-21.8	97	-24.6	98	-19.0	0.2346	0.0181
Week 5	99	-24.5	97	-27.3	98	-20.3	0.0979	0.0057
Week 6[d]	99	-26.7	97	-28.6	98	-21.2	0.0414	0.0061

a: The LS means were the adjusted means from an ANCOVA model of change from baseline, with baseline as a covariate and terms for treatment and region strata. A negative LS mean indicates improvement.
b: The p-values were derived from Student's t tests on estimates of treatment comparisons which were based on LS means.
c: For baseline, N and Mean are provided. Maximum positive score = 210.
d: Primary endpoint.

Using the OC dataset, the PANSS Total Scores at Week 6 were −30.6 in the aripiprazole 10 mg arm, −31.9 in the aripiprazole 30 mg arm, and −22.3 in the placebo arm. The comparison between aripiprazole and placebo was significant at both doses (p = 0.0011 for arip 10 mg vs placebo; p = 0.0002 for arip 30 mg vs placebo). The difference from placebo in mean change from baseline at Week 6 was -8.3.1 (95% CI = -13.3 to -3.37; p = 0.0011) for the aripiprazole 10 mg arm and -9.64 (95% CI = −14.6 to −4.71; p = 0.0002) for the aripiprazole 30 mg arm using OC dataset (see Table 26 in Appendices 10.2).

6.1.4.5.2 Secondary Variables

All secondary variables in this study are non-key secondary variables.

Change from baseline in Children's Global Assessment Scale (CGAS) Score
The CGAS is a measure to provide a global measure of level of functioning in children and adolescents. The measure provides a single global rating only, on scale of 1-100. The mean change from baseline in CGAS Score at Week 6 (LOCF) is presented in Table 10. Both the aripiprazole 10 mg and 30 mg arms showed statistically significant improvements over the placebo arm in the change from baseline in CGAS Score at Week 6 using the LOCF and OC data sets. At Week 6, the mean changes from baseline using LOCF were 14.7, 14.8, and 9.8 in the aripiprazole 10 mg, 30 mg, and placebo arms, respectively (p = 0.0054 for 10 mg vs placebo and p = 0.0044 for 30 mg vs placebo).

Table 10 Mean Change from Baseline to Endpoint in CGAS Score (LOCF)

	Aripiprazole 10 mg N = 97	Aripiprazole 30 mg N = 94	Placebo N = 98	P – value Aripiprazole vs Placebo	
				10 mg	30 mg
Baseline (LS Mean)	46.7	45.6	45.4		
Week 6 (LS Mean)	14.7	14.8	9.8	0.0054	0.0044

Change from Baseline in Clinical Global Impression (CGI) Severity Score
The CGI is one of the most widely used brief assessment tools in psychiatry. This is a three-item scale to measure overall illness severity. The mean change from baseline in the CGI-Severity Score (LOCF) is presented in Table 11. The difference from placebo in mean change from baseline at Week 6 for the aripiprazole 10 mg arm was −0.36 (95% CI = −0.62 to −0.10; p = 0.0071) and for the aripiprazole 30 mg arm was −0.42 (95% CI = −0.68 to −0.16; p = 0.0016). The OC analysis results were consistent with that using LOCF analysis.

Table 11 Mean Change from Baseline to Endpoint in CGI Severity Score (LOCF)

	Aripiprazole 10 mg N = 99	Aripiprazole 30 mg N = 97	Placebo N = 98	P – value Aripiprazole vs Placebo	
				10 mg	30 mg
Baseline (LS Mean)	4.5	4.6	4.6		
Week 6 (LS Mean)	-1.2	-1.3	-0.9	0.0054	0.0044

Change from baseline in PANSS Positive Subscale Score
Improvements over placebo in the mean change from baseline in PANSS Positive Subscale Scores were observed for both the aripiprazole 10 mg and 30 mg arms at all time points using the LOCF and OC data sets.

Using LOCF data set, the difference from placebo in mean change from baseline at Week 6 was −1.95 (95% CI = −3.49 to −0.41; p = 0.0134) for the aripiprazole 10 mg arm and −2.47 (95% CI = −4.02 to −0.92; p = 0.0018) for the aripiprazole 30 mg arm. The OC analysis results were consistent with the findings observed from LOCF analysis. Table 12 shows the mean changes from baseline in the PANSS Positive Subscale Score using the LOCF dataset.

Table 12 Mean Change from Baseline to Endpoint in PANSS Positive Subscale Score (LOCF)

	Aripiprazole 10 mg N = 99	Aripiprazole 30 mg N = 97	Placebo N = 98	P – value Aripiprazole vs Placebo	
				10 mg	30 mg
Baseline (LS Mean)	22.1	23.5	22.9		
Week 6 (LS Mean)	-7.6	-8.1	-5.6	0.0134	0.0018

6.1.4.5.3 Subgroup Analyses

Subgroup analyses were performed to evaluate the mean change from baseline to endpoint in PANSS total score for region, gender, and race for Study 31-03-239. Since this study was an adolescent study (13 to 17 years), no age subgroup analysis was performed. Except the comparisons between aripiprazole 30 mg and placebo for male and for white patients, all other comparisons had nominal p-values >0.05. Since these subgroup analyses are only for the exploratory purpose, the p-values should be interpreted with caution.

6.1.5 Clinical microbiology

Clinical microbiology was not studied in this study and the study was not deemed as necessary.

6.1.6 Efficacy Conclusions

Aripiprazole was effective in the acute treatment of adolescent subjects with schizophrenia at daily doses of 10 mg and 30 mg, as demonstrated by statistically significant improvements compared with placebo in PANSS Total Score at Week 6 (LOCF).

Under FDAMA, 1997, adequate assessment of adolescents (data sufficient to support a labeling claim) might be based on a single study in pediatric patients, together with confirmatory evidence from another source, perhaps adult data for that disorder. This approach is also explicated in the FDA Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Product (Part II, C.2.c). In our PWR on Feb. 11, 2003, we required "a single, independent, adequate and well-controlled clinical trial in adolescent schizophrenia"

"to permit a pediatric claim for a drug already approved in adults". Therefore, the efficacy data from Study 31-03-239 are felt to provide sufficient evidence to support the indication of aripiprazole for the acute schizophrenia treatment in adolescents.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The integrated safety review for this submission is mainly based on safety data from Study 31-03-239, a placebo-controlled, 6-week study. In addition, the safety data from study 31-03-241, an open-label, 6 months safety and tolerability study are also reviewed to assess long-term safety and tolerability of oral aripiprazole and to detect any deaths, and unexpected, serious adverse events. The databases used for this review includes safety reports from each individual study, pertinent .xpt files and narrative summaries.

Since marketing of aripiprazole began in Nov. 2, 2002, its safety profile has been well established, especially in adult population. The safety review from this submission did not find any unexpected serious adverse events and the patterns of common adverse events of aripiprazole remained same as its current labeling.

7.1.1 Deaths

No deaths were reported in Study 31-03-239. One death occurred during Study 31-03-241. Subject 8552084 was accidentally electrocuted after receiving approximately 20 weeks of aripiprazole. This event was considered to be unrelated to treatment.

7.1.2 Other Serious Adverse Events

A total of 8/202 (4.0%) aripiprazole treated subjects and 3/100 (3.0%) placebo-treated subjects experienced SAEs in Study 31-03-239, the majority of which were severe in intensity.

The most commonly reported SAEs overall were psychotic disorder (1 subject in each treatment arm) and schizophrenia (1 subject in each aripiprazole treatment arm). The following SAEs were reported by 1 subject each in the aripiprazole 10 mg arm: extrapyramidal disorder, possible neuroleptic malignant syndrome, aggression, psychotic disorder, schizophrenia, and thrombophlebitis. In the aripiprazole 30 mg arm, the following SAEs were reported by 1 subject each: varicella, depression, psychotic disorder, schizophrenia, and suicidal ideation. In the placebo arm, intentional overdose, overdose, psychotic disorder, and suicide attempt were reported by 1 subject in each SAE. Table 13 presents all SAEs reported in the study.

Table 13 All Serious Treatment-emergent Adverse Events

Class and MedDRA Preferred Term	Aripiprazole 10 mg (N = 100) n (%)	Aripiprazole 30 mg (N = 102) n (%)	Placebo (N = 100) n (%)	Total (N = 302) n (%)
Total subjects with at least one SAE	4 (4.0)	4 (3.9)	3 (3.0)	11 (3.6)
Infections and Infestations				
Varicella	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.3)
Injury, Poisoning, and Procedural Complications				
Intentional overdose	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.3)
Overdose	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.3)
Nervous System Disorders				
Extrapyramidal disorder	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.3)
Neuroleptic malignant syndrome [a]	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.3)
Psychiatric Disorders				
Aggression	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.3)
Depression	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.3)
Psychotic disorder	1 (1.0)	1 (1.0)	1 (1.0)	3 (1.0)
Schizophrenia	1 (1.0)	1 (1.0)	0 (0.0)	2 (0.7)
Suicidal ideation	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.3)
Suicide attempt	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.3)
Vascular Disorders				
Thrombophlebitis	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.3)

In Study 31-03-241 (long term safety study), 22 (7.8%) subjects experienced SAEs during the study. The pattern of SAEs matches that observed in Study 31-03-239. Worsening or exacerbation of schizophrenia (2.1%) was the most common SAE, followed by psychotic disorder (1.4%), aggression (0.7%), and suicidal ideation (0.7%). No unexpected SAEs were observed.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of Dropouts

Overall profile of dropouts is summarized in Table 14. The overall discontinuation rate was 14.6%. AEs and subject withdrawal of consent were the most common reasons for discontinuation. A total of 7/100 (7.0%), 4/102 (3.9%), and 2/100 (2.0%) subjects withdrew due to AEs and 4/100 (4.0%), 12/102 (11.8%), and 5/100 (5.0%) subjects withdrew consent in the aripiprazole 10 mg, 30 mg, and placebo arms, respectively. Additionally, 5/100 (5.0%) subjects withdrew due to lack of efficacy in the aripiprazole 10 mg arm as determined by the investigator, compared with 1/102 (1.0%) in the aripiprazole 30 mg arm and 1/100 (1.0%) in the placebo arm.

Table 14 Subject Discontinuation

	Aripiprazole 10 mg N=100	Aripiprazole 30 mg N=102	Placebo N=100	Total N=302
Discontinued N (%)	16 (16.0)	18 (17.6)	10 (10.0)	44 (14.6)
Adverse event	7 (7.0)	4 (3.9)	2 (2.0)	13 (4.3)
Lost to follow up	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.3)
Subject withdrew consent	4 (4.0)	12 (11.8)	5 (5.0)	21 (7.0)
Protocol deviation	0 (0.0)	1 (1.0)	1 (1.0)	2 (0.7)
Lack of efficacy	5 (5.0)	1 (1.0)	1 (1.0)	7 (2.3)

7.1.3.2 Adverse events associated with dropouts

Table 15 presents all TEAEs resulting in discontinuation of study medication. A total of 13/302 (4.3%) subjects discontinued study medication due to a TEAE: 7/100 (7.0%) in the aripiprazole 10 mg arm, 4/102 (3.9%) in the aripiprazole 30 mg arm, and 2/100 (2.0%) in the placebo arm. Aripiprazole 10 mg arm was associated with higher discontinuation rate due to AEs. The majority AEs were moderate to severe in intensity.

The most commonly reported TEAEs resulting in discontinuation of study medication were psychotic disorder and schizophrenia. Other TEAEs resulting in discontinuation of study medication were: dystonia, somnolence, anxiety, and hypomania in the aripiprazole 10 mg arm; nausea and varicella in the aripiprazole 30 mg arm; and overdose in the placebo arm.

Table 15 TEAEs Resulting in Discontinuation of Study Medication

Class and MedDRA Preferred Term	**Aripiprazole 10 mg (N = 100) n (%)**	**Aripiprazole 30 mg (N = 102) n (%)**	**Placebo (N = 100) n (%)**	**Total (N = 302) n (%)**
Total subjects who discontinued due to AE	7 (7.0)	4 (3.9)	2 (2.0)	13 (4.3)
Gastrointestinal Disorders				
Nausea	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.3)
Infections and Infestations				
Varicella	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.3)
Injury, Poisoning, and Procedural Complications				
Overdose	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.3)
Nervous System Disorders				
Dystonia	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.3)
Somnolence	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.3)
Psychiatric Disorders				
Anxiety	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.3)
Hypomania	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.3)
Psychotic disorder	1 (1.0)	1 (1.0)	1 (1.0)	3 (1.0)
Schizophrenia	2 (2.0)	1 (1.0)	0 (0.0)	3 (1.0)

7.1.3.3 Other significant adverse events

TEAEs associated with EPS-related symptoms are listed in Table 16. The most commonly reported TEAEs associated with EPS-related symptoms (≥ 5% incidence in any treatment group) were akathisia (5.0% in the aripiprazole 10 mg, 11.8% in the aripiprazole 30 mg, and 5.0% in the placebo); extrapyramidal disorder (13.0% in the aripiprazole 10 mg, 21.6% in the aripiprazole 30 mg arm, and 5.0% in the placebo); and tremor (2.0% in the aripiprazole 10 mg, 11.8% in the aripiprazole 30 mg arm, and 2.0% in the placebo). The incidence of these TEAEs, as well as that for salivary hypersecretion, gait disturbance, drooling, dyskinesia, and myoclonus increased with dose of aripiprazole. The majority of EPS related events were mild or moderate in severity and only one event (dystonia, 30 mg arm) led to discontinuation from the study.

Table 16 TEAEs Associated with EPS Symptoms

Class and MedDRA Preferred Term	Aripiprazole 10 mg (N = 100) n (%)	Aripiprazole 30 mg (N = 102) n (%)	Placebo (N = 100) n (%)	Total (N = 302) n (%)
Gastrointestinal Disorders				
Salivary hypersecretion	1 (1.0)	3 (2.9)	1 (1.0)	5 (1.7)
General Disorders and Administration Site Conditions				
Gait disturbance	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.3)
Musculoskeletal and Connective Tissue Disorders				
Joint stiffness	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.3)
Muscle rigidity	1 (1.0)	1 (1.0)	0 (0.0)	2 (0.7)
Nervous System Disorders				
Akathisia	5 (5.0)	12 (11.8)	5 (5.0)	22 (7.3)
Drooling	0 (0.0)	3 (2.9)	0 (0.0)	3 (1.0)
Dyskinesia	1 (1.0)	2 (2.0)	0 (0.0)	3 (1.0)
Dystonia	3 (3.0)	1 (1.0)	0 (0.0)	4 (1.3)
Extrapyramidal disorder	13 (13.0)	22 (21.6)	5 (5.0)	40 (13.2)
Hyperkinesia	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.3)
Myoclonus	0 (0.0)	1 (1.0)	0 (0.0)	1 (0.3)
Neuroleptic malignant syndrome[a]	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.3)
Tremor	2 (2.0)	12 (11.8)	2 (2.0)	16 (5.3)

Compared with adult population, there were more EPS-related symptoms reported in this study. For aripiprazole treatment, the incidence of EPS-related events (excluding akathisia) in adults ranged from 13 to 15% in short-term trials of schizophrenia and bipolar mania compared to 25% in Study 31-03-239. For akathisia-related events, the incidence in adults ranged from 8 to 15% versus 9% in adolescents.

7.1.4 Other Search Strategies

No other search strategies were warranted.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Adverse events were assessed at all visits. In addition, the site called the subject on Day 4, between the visits on Day 1 and Day 7, to assess adverse events during the forced titration period. In order to avoid bias in eliciting adverse events, subjects were asked non-leading question, such as, "How are you feeling?" All adverse events reported by the subject must be recorded on the source documents and case report forms provided by the Sponsor.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

All AEs were coded from verbatim terms to System Organ Class and preferred terms using the Medical Dictionary for Regulatory Activities (MedDRA), Version 9.1.

7.1.5.3 Incidence of common adverse events

The percentage of subjects who experienced at least one TEAE was slightly higher in the aripiprazole arms than in the placebo arm (71%, 72.5% and 57.0% in arip10, 30 mg, and the placebo arm respectively). A greater percentage of subjects (7.0%) in the aripiprazole 10 mg arm experienced severe TEAEs than did subjects in the aripiprazole 30 mg arm (3.9%) or in the placebo arm (3.0%). The majority of TEAEs were mild or moderate in severity.

7.1.5.4 Common adverse event tables

Table 17 summarizes the most commonly reported TEAEs by ≥ 5% incidence in any treatment arm.

Table 17 Most Commonly Reported TEAEs by ≥ 5% in Any Treatment Group

Class and MedDRA Preferred Term	Aripiprazole 10 mg (N = 100) n (%)	Aripiprazole 30 mg (N = 102) n (%)	Placebo (N = 100) n (%)	Total (N = 302) n (%)
Total subjects with at least one TEAE	71 (71.0)	74 (72.5)	57 (57.0)	202 (66.9)
Gastrointestinal Disorders				
Nausea	9 (9.0)	10 (9.8)	6 (6.0)	25 (8.3)
Vomiting	5 (5.0)	3 (2.9)	5 (5.0)	13 (4.3)
Infections and Infestations				
Nasopharyngitis	5 (5.0)	5 (4.9)	4 (4.0)	14 (4.6)
Nervous System Disorders				
Akathisia	5 (5.0)	12 (11.8)	5 (5.0)	22 (7.3)
Dizziness	7 (7.0)	4 (3.9)	3 (3.0)	14 (4.6)
Extrapyramidal disorder	13 (13.0)	22 (21.6)	5 (5.0)	40 (13.2)
Headache	16 (16.0)	11 (10.8)	10 (10.0)	37 (12.3)
Somnolence	11 (11.0)	22 (21.6)	6 (6.0)	39 (12.9)
Tremor	2 (2.0)	12 (11.8)	2 (2.0)	16 (5.3)
Psychiatric Disorders				
Agitation	1 (1.0)	3 (2.9)	5 (5.0)	9 (3.0)
Insomnia	11 (11.0)	10 (9.8)	15 (15.0)	36 (11.9)

7.1.5.5 Identifying common and drug-related adverse events

Common adverse events were identified by that the occurrence rate was at least 2% or more in treatment arms.

Any event with onset after the first dose of aripiprazole or any event which was ongoing from baseline and became serious, worsened, was classified as related to study drug, or resulted in death, discontinuation, interruption or reduction of dose was considered to be treatment-emergent.

7.1.5.6 Additional analyses and explorations

7.1.5.6.1 Extrapyramidal Symptom Rating Scales

The Simpson-Angus Scale (SAS) total score, Barnes Akathisia Rating Scale (BARS) global score and Abnormal Involuntary Movement Scale (AIMS) movement rating score were conducted to assess extrapyramidal adverse events. The data were analyzed by week in both LOCF and OC population. Although some differences between the aripiprazole treatment arms and placebo arms reached statistical significance, these changes were not considered clinically meaningful.

Change from Baseline in SAS Total Score
At baseline, the mean SAS Total Scores ranged from 10.6 to 11.1 across treatment arms. Statistically significant mean increases in parkinsonian symptoms compared to placebo were

observed in the aripiprazole 10 mg arm at Weeks 4, 5, and 6, and for placebo over the aripiprazole 30 mg arm at Weeks 2, 3, 4, 5, and 6 (LOCF and OC).

Change from Baseline in BARS Global Score
At baseline, the mean BARS Global Score was 0.1 across treatment arms. A statistically significant mean increase in akathisia symptoms compared to placebo was observed in the aripiprazole 30 mg arm at Week 2 using the LOCF data set.

Change from Baseline in AIMS Movement Rating Score
Small improvements (ie, decreases) in the mean AIMS Movement Rating Scores were seen in the aripiprazole 10 mg and 30 mg arms using the LOCF and OC datasets. The greatest mean changes (decrease) from baseline were in the aripiprazole 10 mg arm at Weeks 4, 5, and 6; the difference from placebo was statistically significant at Week 5 ($p = 0.0486$; LOCF). No statistically significant differences between treatment arms were observed using the OC dataset.

7.1.6 Less Common Adverse Events

No less common adverse events of significant concern were identified in these studies.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Routine safety laboratory including hemotology, serum chemistry, and urinalysis were conducted during the study. Other laboratory tests including serum insulin, fasting insulin, and prolactin were also performed. Mean change from baseline to endpoint, treatment-emergent abnormalities at any time and treatment-emergent potentially clinically significant abnormalities for each laboratory analyte were analyzed separately.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Study 31-03-239 is the only acute, controlled study submitted to this sNDA. Therefore, only laboratory data from Study 31-03-239 were reviewed in detail in this safety review. Safety data from Study 31-03-241, an open label, long term safety study, were used to detect rare, and unexpected serious clinically significant laboratory abnormalities.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.3.1 Analyses focused on measures of central tendency

Serum Chemistry
No clinically relevant mean changes were observed for any of the serum chemistry laboratory tests. There were no dose-related trends observed in the serum chemistry test abnormalities

reported as TEAEs. None of these TEAEs were reported as SAEs or resulted in discontinuation of study medication.

Hematology
No clinically relevant mean changes were observed for any of the hematology laboratory tests. Two abnormal hematology laboratory test results were reported as TEAEs: increased eosinophil count and increased glycosylated haemoglobin (1 subject each in the aripiprazole 10 mg arm). Neither of these TEAEs was reported as an SAE or resulted in discontinuation of study medication.

Urinalysis
No clinically relevant mean changes were observed for any of the urinalysis laboratory tests. One abnormal urinalysis laboratory test results was reported as a TEAE: asymptomatic bacteriuria (2 subjects in the placebo arm). This TEAE was not an SAE nor did it result in discontinuation of study medication.

Insulin
No clinically relevant mean changes were observed in the insulin or fasting insulin results. Two abnormal insulin laboratory test results were reported as TEAEs: increased blood insulin (2 subjects in the aripiprazole 10 mg arm) and hyperinsulinemia (1 subject in the aripiprazole 10 mg arm). Neither of these TEAEs was reported as an SAE or resulted in discontinuation of study medication.

Prolactin
A mean decrease in prolactin levels relative to baseline was observed overall across all treatment groups. The mean change from baseline to endpoint in prolactin levels was -8.82 ng/mL, -11.94 ng/mL, and -16.74 ng/mL in the placebo, aripiprazole 10 mg, and aripiprazole 30 mg arms, respectively.

When analyzed by gender, similar pattern were observed for males (−4.21 ng/mL, −9.62 ng/mL, and −14.69 ng/mL in the placebo, arip 10 mg, and arip 30 mg arms, respectively). For females, the decreases in prolactin levels were greater than for males in all treatment arms, especially in placebo arm (−15.81 ng/mL, −13.70 ng/mL, and −20.62 ng/mL in the placebo, arip 10 mg, and arip 30 mg arms, respectively).

The clinical significance of decrease in prolactin level is unclear. Since majority patients have been exposed to different antipsychotics right before this study (3 days washout period before given study medications and 74% patients have received treatment for previous episodes), the decrease in prolactin level in this study may be partly caused by discontinuation of prolactin increasing antipsychotics, such as risperidone.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

Table 18 summarizes incidence of potentially clinically significant laboratory test abnormalities. The most commonly reported potentially clinically significant laboratory test abnormalities (by ≥

3% incidence in any treatment group) were: ALT, total bilirubin, total CPK, eosinophils (%) and prolactin. Overall, no clinically meaningful trends were observed for any of the potentially clinically significant laboratory test abnormalities.

Table 18 Incidence of Potentially Clinically Significant Laboratory Test Abnormalities

Test (Units)[a]	Aripiprazole 10 mg (N = 100)		Aripiprazole 30 mg (N = 102)		Placebo (N = 100)		Total (N = 302)	
	Ne[a]	n (%)[b]	Ne[a]	n (%)[b]	Ne[a]	n (%)[b]	Ne[a]	n (%)[b]
Chemistry								
ALT (IU/L)	98	3 (3.1)	95	2 (2.1)	96	0 (0.0)	289	5 (1.7)
AST (IU/L)	98	2 (2.0)	95	1 (1.1)	96	0 (0.0)	289	3 (1.0)
Bilirubin, total (mg/dL)	98	1 (1.0)	95	4 (4.2)	96	2 (2.1)	289	7 (2.4)
CPK, total (IU/L)	98	5 (5.1)	95	7 (7.4)	96	5 (5.2)	289	17 (5.9)
Potassium (mEq/L)	98	0 (0.0)	95	0 (0.0)	96	1 (1.0)	289	1 (0.3)
Uric acid (mg/dL)	98	1 (1.0)	95	0 (0.0)	96	1 (1.0)	289	2 (0.7)
Hematology								
Eosiniphils (%)	95	7 (7.4)	93	2 (2.2)	93	3 (3.2)	281	12 (4.3)
Hematocrit (%)	95	0 (0.0)	93	0 (0.0)	94	1 (1.1)	282	1 (0.4)
Hemoglobin (g/dL)	95	2 (2.1)	93	0 (0.0)	94	1 (1.1)	282	3 (1.1)
WBC (thous/μL)	95	0 (0.0)	93	1 (1.1)	94	1 (1.1)	282	2 (0.7)
Other								
Prolactin (ng/mL)	98	3 (3.1)	95	0 (0.0)	96	6 (6.3)	286	9 (3.1)

7.1.3.3.3 Marked outliers and dropouts for laboratory abnormalities

No any SAEs were caused by laboratory abnormalities and no cases were discontinued due to laboratory abnormalities.

7.1.7.4 Additional analyses and explorations

Metabolic Syndrome Evaluation
The analyses on the mean changes from baseline in fasting triglycerides, fasting HDL-C levels, fasting glucose levels, waist circumference, BMI and blood pressure were performed. Overall, no clinically meaningful changes from baseline were observed in any of the above metabolic syndrome evaluation parameters for males or females.

The incidences of metabolic syndrome abnormalities were also analyzed. Overall at the last visit, no clinically meaningful trends were observed in the incidences of abnormalities for fasting triglyceride levels, fasting HDL-C levels, fasting glucose levels, supine systolic or diastolic BP, and standing systolic and diastolic BP. The fasting triglyceride levels, fasting HDL-C levels, fasting glucose levels and BMI for all subjects were presented in Table 20. The criteria for above metabolic measures are presented in Table 19.

Table 19 Criteria for Metabolic Syndrome Abnormalities

Parameter	Age	Criterion Value
Serum fasting triglycerides (mg/dL)	12 – 19 years	≥ 110 mg/dl
Serum fasting HDL-C (mg/dL)	12 – 19 years	≤ 40 mg/dL
Serum fasting glucose (mg/dL)	12 – 19 years	≥ 110 mg/dL
BMI	12 – 19 years	> 95th percentile within the same age and gender population

Table 20 Incidence of Fasting Triglyceride, HDL, Glucose Abnormalities for All Subjects

Parameter	Visit	Aripiprazole 10 mg N=100		Aripiprazole 30 mg N=100		Placebo N=100	
		N	n (%)	N	n (%)	N	n (%)
Fasting Triglyceride (mg/dL)	Baseline	50	17(34.0)	49	17(34.7)	51	22(43.1)
	Day 42	51	17(33.3)	40	12(30.0)	44	16(36.4)
	Last visit	59	18(30.5)	49	16(32.7)	50	17(34.0)
Fasting HDL-C level (mg/dL)	Baseline	50	13(26.0)	49	10(20.4)	51	16(31.4)
	Day 42	51	13(25.5)	40	10(25.0)	44	16(36.4)
	Last visit	59	14(23.7)	49	12(24.5)	50	20(40.0)
Fasting glucose level (mg/dL)	Baseline	69	4(5.8)	69	1(1.4)	70	4(5.7)
	Day 42	73	2(2.7)	70	0(0.0)	75	2(2.7)
	Last visit	86	2(2.3)	79	0(0.0)	88	2(2.3)
BMI (kg/cm^2)	Baseline	100	20(20)	102	13(12.7)	100	13(13.0)
	Day 42	84	12(14.3)	84	10(11.9)	89	12(13.5)
	Last visit						

N is the total number of subjects with postbaseline results at the visit.
n is the number of subjects meeting the criteria for potential clinical significance.

7.1.7.5 Special Assessments

No special assessments were warranted in this study.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

The potential treatment effect on mean change from baseline to Day 42 and last visit, and on treatment-emergent potentially clinically significant abnormalities in vital signs including standing and supine blood pressure, standing and supine heart rate, body temperature and weight were summarized and assessed across treatment groups.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

Study 31-03-239 is the only acute, controlled study submitted to this sNDA. Therefore, only vital signs data from Study 31-03-239 were reviewed in detail in this safety review. Safety data from Study 31-03-241, an open label, long term safety study, were used to detect rare, and unexpected serious, clinically significant vital sign abnormalities.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

The analyses on the mean changes from baseline in vital signs parameters (weight, BMI, waist circumference, body temperature, respiration rate, supine and standing heart rate, supine and standing BP) were performed. No clinically relevant mean changes from baseline were observed in vital signs parameters.

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

The following abnormal vital sign findings were reported as TEAEs: palpitations and postural orthostatic tachycardia syndrome (1 each in the aripiprazole 30 mg arm); tachycardia (2 in the aripiprazole 10 mg arm); pyrexia (1 in the aripiprazole 10 mg arm, 3 in the aripiprazole 30 mg arm, and 2 in the placebo arm); increased body temperature (1 in the aripiprazole 10 mg arm and 1 in the placebo arm); hot flush (1 in the aripiprazole 10 mg arm); hypotension (2 in the aripiprazole 30 mg arm and 1 in the placebo arm); and orthostatic hypotension (3 in the aripiprazole 30 mg arm).

At the last visit, the percentage of subjects who experienced a potentially clinically significant weight gain (≥ 7% weight gain compared to baseline) was 4/99 (4.0%) in the aripiprazole 10 mg arm, 5/97 (5.2%) in the aripiprazole 30 mg arm, and 1/98 (1.0%) in the placebo arm. The percentage of subjects who experienced a potentially clinically significant weight loss (≥ 7% weight loss compared to baseline) at the last visit was 3/99 (3.0%) in the aripiprazole 10 mg arm, 2/97 (2.1%) in the aripiprazole 30 mg arm, and 6/98 (6.1%) in the placebo arm.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

None of treatment-emergent vital signs abnormalities were reported as SAEs or resulted in discontinuation of study medication.

7.1.8.4 Additional analyses and explorations

Weight and BMI Z-scores

The mean changes from baseline for weight (see Table 21) and BMI z-scores (see Table 22) for Day 42 and last visit were within 0.5 SD of the general population for all three treatment arms, and the changes from baseline were negligible. At the last visit, the mean (SD) in weight z-score was 0.00 (0.28) with a range of −1.31 to 1.54 in the aripiprazole 10 mg arm; 0.00 (0.20) with a range of −0.76 to 0.46 in the aripiprazole 30 mg arm; and −0.11 (0.22) with a range of −0.98 to 0.39 in the placebo arm. At the last visit, the mean (SD) in BMI z-score was 0.01 (0.26) with a range of −1.08 to 1.07 in the aripiprazole 10 mg arm; 0.01 (0.25) with a range of −1.07 to 0.80 in the aripiprazole 30 mg arm; and −0.12 (0.27) with a range of −0.99 to 0.56 in the placebo arm.

Similar results were observed for the mean change from baseline in BMI z-scores for males and for females.

Table 21 Mean Change from Baseline in Weight Z-scores

Treatment	Visit	n	Mean (SD)	Change from Baseline		
				n	Mean (SD)	Range
Arip 10 mg	Baseline	100	0.14 (1.42)			
	Day 42	84	0.14 (1.27)	84	0.03 (0.26)	-0.56 – 1.54
	Last Visit	99	0.13 (1.37)	99	0.00 (0.28)	-1.31 – 1.54
Arip 30 mg	Baseline	102	0.26 (1.28)			
	Day 42	84	0.25 (1.31)	84	-0.00 (0.21)	-0.76 – 0.46
	Last Visit	97	0.28 (1.28)	97	0.00 (0.20)	-0.76 – 0.46
Placebo	Baseline	100	0.25 (1.14)			
	Day 42	89	0.13 (1.19)	89	-0.12 (0.22)	-0.98 – 0.39
	Last Visit	98	0.17 (1.17)	98	-0.11 (0.22)	-0.98 – 0.39

Table 22 Mean Change from Baseline in Body Mass Index Z-scores

Treatment	Visit	n	Mean (SD)	Change from Baseline		
				n	Mean (SD)	Range
Arip 10 mg	Baseline	100	0.35 (1.30)			
	Day 42	84	0.31 (1.19)	84	0.03 (0.24)	-0.60 – 1.07
	Last Visit	99	0.34 (1.26)	99	0.01 (0.26)	-1.08 – 1.07
Arip 30 mg	Baseline	102	0.39 (1.08)			
	Day 42	84	0.38 (1.05)	84	0.01 (0.26)	-1.07 – 0.80
	Last Visit	97	0.41 (1.03)	97	0.01 (0.25)	-1.07 – 0.80
Placebo	Baseline	100	0.35 (1.12)			
	Day 42	89	0.21 (1.20)	89	-0.13 (0.27)	-0.99 – 0.56
	Last Visit	98	0.25 (1.18)	98	-0.12 (0.27)	-0.99 – 0.56

In the 6-month, long-term safety study (31-03-241), the mean changes from baseline for weight, BMI, and height z-scores for each visit were within 0.5 standard deviations of the general population. This was also true of BMI z-scores when analyzed by gender. No clinically meaningful changes were observed in weight z-scores or BMI z-scores or in the overall evaluation.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

Mean change, treatment-emergent ECG abnormalities, and treatment-emergent potentially clinically significant ECG abnormalities were summarized and compared across treatment groups. No clinically meaningful ECG abnormalities were observed.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

Study 31-03-239 is the only acute, controlled study submitted to this sNDA. Therefore, only ECG data from Study 31-03-239 were reviewed in detail in this safety review. Safety data from

Study 31-03-241, an open label, long term safety study, were used to detect rare and unexpected serious clinically significant ECG abnormalities.

For the analysis of QT and QTc the following correction methods were used by the sponsor:

- QTcB is the corrected (for heart rate) QT interval by the Bazett formula: $QTcB=QT/(RR)_{0.5}$
- QTcF is the corrected (for heart rate) QT interval by the Fridericia formula: $QTcF=QT/(RR)_{0.33}$, and
- QTcE is the corrected (for heart rate) QT interval by the general fractional exponent correction method, i.e., $QTcF= QT/(RR)_k$. The value of k will be determined by fitting the regression equation log(QT)=constant + klog(RR) using the pre-treatment (QT,RR) data of all subjects.

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency

The changes from baseline in ECG parameters (including ventricular rate, PR interval, RR interval, QRS interval, and QT interval) were analyzed and no clinically significant mean changes from baseline were observed.

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

The incidences of potentially clinically significant changes in ECG parameters are summarized in Table 23. Overall, no clinically meaningful trends were observed for any of the potentially clinically significant changes in ECG parameters.

Table 23 Incidence of Potentially Clinically Significant Changes in ECG Parameters

Type/Abnormality	Aripiprazole 10 mg (N = 100)		Aripiprazole 30 mg (N = 102)		Placebo (N = 100)		Total (N = 302)	
	Ne[a]	n (%)[b]	Ne[a]	n (%)[b]	Ne[a]	n (%)[b]	Ne[a]	n (%)[b]
Rhythm								
Sinus bradycardia	92	2 (2.2)	92	1 (1.1)	89	1 (1.1)	273	4 (1.5)
Supraventricular premature beat	92	0 (0.0)	92	2 (2.2)	89	2 (2.2)	273	4 (1.5)
ST/T Morphology								
Myocardial ischemia	92	1 (1.1)	92	0 (0.0)	89	0 (0.0)	273	1 (0.4)
QTcB	92	2 (2.2)	92	3 (3.3)	89	3 (3.4)	273	8 (2.9)

[a] Ne is the total number of subjects with at least one postbaseline numeric result for the given parameter.
[b] n is the number of subjects with a potentially clinically significant ECG test abnormality.

The following ECG abnormalities were reported as TEAEs: sinus bradycardia (1 subject each in the aripiprazole 10 mg and 30 mg arms); supraventricular extrasystoles (1 subject each in the aripiprazole 30 mg arm and the placebo arm); wandering pacemaker (1 subject in the 30 mg aripiprazole arm); abnormal electrocardiogram T wave (1 subject in the placebo arm).

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

None of the ECG abnormalities were reported as SAEs or resulted in discontinuation of study medication.

7.1.9.4 Additional analyses and explorations

Additional ECG QT Interval Analyses

A summary of mean change from baseline in QT and QTc interval at Day 42 and last visit is presented in Table 24. Overall, greater decreases in mean QT and QTc intervals from baseline to Day 42 and the last visit were seen in the 30 mg aripiprazole arm compared to the placebo arm. Differences between changes from baseline in the 30 mg aripiprazole arm and placebo arm were statistically significant for all QT and QTc variables at both time points. I discussed this issue (QT shortening) with Dr. Stephen Grant, a medical reviewer in QT-team, the Division of Cardiovascular-Renal Drug Products (DCRDP), and Dr. Norman Stockbridge, director of DCRDP. They felt that at this time point no QT consultation is necessary and no any regulatory actions are recommended because the QT interval shortness in this study were very small (< 7 Msec) and the clinical significance of shortening QT interval is remained unclear at this time.

Table 24 Mean Change from Baseline in QT and QTc Intervals at Day 42 and Last Visit (Msec)

Visit/Week	Aripiprazole 10 mg N	Aripiprazole 10 mg LS Mean[a]	Aripiprazole 30 mg N	Aripiprazole 30 mg LS Mean[a]	Placebo N	Placebo LS Mean[a]	P-value[b] Aripiprazole 10 mg vs placebo	P-value[b] Aripiprazole 30 mg vs placebo
QT								
Day 42	81	1.66	83	-1.14	80	7.75	0.0804	0.0106
Last Visit	91	-0.21	92	-2.29	87	5.73	0.0742	0.0159
QTcB[c]								
Day 42	81	-1.06	83	-6.93	80	0.34	0.5799	0.0039
Last Visit	91	-0.98	92	-5.58	87	-0.02	0.6881	0.0199
QTcF[c]								
Day 42	81	0.08	83	-4.82	80	2.87	0.1444	<.0001
Last Visit	91	-0.62	92	-4.37	87	1.94	0.1564	0.0005
QTcN[c]								
Day 42	81	-0.27	83	-5.22	80	2.47	0.1612	<.0001
Last Visit	91	-0.78	92	-4.54	87	1.65	0.1872	0.0008
QTcE[c]								
Day 42	81	0.03	83	-4.63	80	3.00	0.1216	<.0001
Last Visit	91	-0.64	92	-4.21	87	2.05	0.1360	0.0006

7.1.10 Immunogenicity

Immunogenicity was not studied in these studies.

7.1.11 Human Carcinogenicity

Human carcinogenicity was not studied in these studies.

7.1.12 Special Safety Studies

No special safety studies were deemed necessary.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Withdrawal phenomena and/or abuse potential were not studied in these studies.

7.1.14 Human Reproduction and Pregnancy Data

No pregnancies were reported in this study.

7.1.15 Assessment of Effect on Growth

The mean changes from baseline for weight and BMI z-scores (see 7.1.8.4 Additional Analyses and Exploration/Weight and BMI Z-scores Table 21 and Table 22) for each visit in Study 31-03-239 were within 0.5 SD of the general population for all three treatment arms, and the changes from baseline were negligible. Therefore, no significant effect on growth from aripiprazole acute treatment was observed.

In the 6-month, long-term safety study (31-03-241), the mean changes from baseline for weight, BMI, and height z-scores for each visit were within 0.5 standard deviations of the general population. Because there was no control arm in this study, it is difficult to interpret the data from this study.

7.1.16 Overdose Experience

No aripiprazole overdose experience was reported in these studies.

7.1.17 Postmarketing Experience

Since aripiprazole was approved for marketing in Nov. 2002, it was estimated that 42,170 patients aged 1-20 years have received aripiprazole from 19 Nov. 2002 to 16 Aug. 2003. Aripiprazole naïve patients for whom at least one Abilify prescription had been filled were estimated to be (b) (4) . In addition, based on post-marketing safety surveillance information from 423 pediatric aripiprazole spontaneous cases received during the period starting 19-NOV-2002 and ending 09-JAN- 2005, aripiprazole doses ranging from 3.5 mg to 30 mg were reported in pediatric patients ranging from 2.5 to 17 years of age. The pattern of adverse event frequency seen in the pediatric patients is similar to what has been observed in the adult population, and as such, does not reflect a medically significant deviation from the known profile of aripiprazole.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

Study 31-03-239 is a multicenter, randomized, double-blind, placebo-controlled trial designed to assess the safety and efficacy of two fixed doses of aripiprazole (10 mg and 30 mg) compared to placebo in adolescent patients, ages 13 to 17 years, with a DSM-IV diagnosis of schizophrenia.

A total of 302 subjects were randomized and treated in this study: 100/302 (33.1%) in the aripiprazole 10 mg arm, 102/302 (33.8%) in the aripiprazole 30 mg arm, and 100/302 (33.1%) in the placebo arm. Of these, 93/302 (30.8%) were randomized in the US, 141/302 (46.7%) were randomized in Europe, and 68/302 (22.5%) were randomized in other regions. All randomized subjects were included in the efficacy and safety analyses.

A total of 258/302 (85.4%) subjects completed the study: 84/100 (84.0%) in the aripiprazole 10 mg arm, 84/102 (82.4%) in the aripiprazole 30 mg arm, and 90/100 (90.0%) in the placebo arm.

7.2.1.2 Demographics

The three treatment arms in Study 31-03-239 were demographically similar and had similar baseline disease characteristics. The majority of subjects were male (171/302, 56.6%), and Caucasian (180/302, 60.0%). Male and Caucasian population were slightly lower respectively in Aripiprazole 10 mg arm (45%, 54%) compare to Aripiprazole 30 mg (63.7%, 64.0%) or placebo (61%, 60%) arm. The mean age was 15.5 years. The baseline disease severity was comparable across all treatment arms. The mean PANSS Total Score and CDRS-R Suicidal Ideations Score was 94.1 and 1.3, respectively. A total of 223/302 (74.0%) subjects had received treatment for previous episodes.

7.2.1.3 Extent of exposure (dose/duration)

A total of 202 subjects were exposed to aripiprazole in Study 31-03-239: 100 in the 10 mg arm at average doses ranging from 6.2 mg to 10.0 mg, and 102 in the 30 mg arm at average doses ranging from 6.9 mg to 30.0 mg. A total of 100 subjects were exposed to placebo. The percentage of subjects exposed to study drug for 36 to 42 days was 86/100 (86.0%) in the aripiprazole 10 mg arm at an average dose of 9.5 mg; 84/102 (82.4%) in the aripiprazole 30 mg arm at an average dose of 27.8 mg; and 90/100 (90.0%) in the placebo arm. Approximately one-third of subjects in all treatment groups were exposed to study medication beyond the planned 42-day treatment period. Table 25 summarizes subject exposure to aripiprazole or placebo in Study 31-03-239.

Table 25 Extent of Exposure to Study Medication in Study 31-03-239

Study Days	Aripiprazole 10 mg N = 100		Aripiprazole 30 mg N = 102		Placebo N = 100
	n (%)	Average dose (mg)	n (%)	Average dose (mg)	n (%)
36 - 42 Days	86 (86.0)	9.5	84 (82.4)	27.8	90 (90.0)
Fixed dose period	99 (99.0)	9.8	94 (92.2)	28.9	97 (97)
Overall	100 (100)	8.9	102 (100.0)	22.5	100 (100.0)

As of the clinical data cut-off date of 09 Nov 2006, long-term safety data were available from 281 adolescent subjects with schizophrenia that received oral aripiprazole in Studies 31-03-239 and/or 31-03-241. Of these subjects, 147 (52.3%) were exposed to aripiprazole for ≥ 26 weeks and 196 (69.8%) for > 20 weeks. This adolescent population represents a cumulative exposure to aripiprazole of 119 subject-years. Subjects in the long-term analysis received an average aripiprazole dose of 16.1 mg daily, ranging from 2.0 to 28.8 mg. Of the subjects treated for ≥ 26 weeks, 34.0% received an average daily dose of ≥ 20 mg.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

No other studies were conducted to evaluate the safety for this submission.

7.2.2.2 Postmarketing experience

See 7.1.17 Postmarketing experience

7.2.2.3 Literature

See 8.6 Literature Review

7.2.3 Adequacy of Overall Clinical Experience

Overall clinical experience was adequate to evaluate the efficacy and safety of aripiprazole in adolescents.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

No animal and/or in vitro tests were conducted for this submission, nor were the studies deemed necessary.

7.2.5 Adequacy of Routine Clinical Testing

Routine clinical testing in this submission was adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Study 31-03-238, a pharmacokinetic study, is submitted to this sNDA and Andre J. Jackson, PhD is the primary Bio-Pharm reviewer for this study. Up to time of completion of this review, Dr. Jackson's review is still pending.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

There are no recommendations for further study.

7.2.8 Adequacy Assessment of Quality and Completeness of Data

An audit of the Case Report Forms (CRFs), Narrative Summaries and adverse event data listing was conducted for one patient (subject 03239-356-3045, 10% of the 10 patients with submitted CRFs), whom I randomly selected from the database from Study 31-03-239. The AE data listings examined were AE0.xpt from 31-03-239 datasets. The consistency of adverse event data across CRFs, Narrative Summaries and AE0.xpt file was examined. An examination of the AE information across these sources for this subject revealed reasonable consistency and completeness.

Two study sites (Site 074 and 104) in Study 31-03-239 were selected for scientific inspection by DSI. The inspection found a few minor deficiencies of data in each study site. But, the inspector felt that the deficiencies were unlikely to have an effect on data reliability.

7.2.9 Additional Submissions, Including Safety Update

No additional safety submissions, including safety update were submitted to this NDA during review period.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

Based on a comparison of the results of five short-term adult studies in schizophrenia with the results of this pediatric schizophrenia study, the safety profile of aripiprazole in adolescents with the diagnosis of schizophrenia is comparable to the adult schizophrenia population, with the exception of dose-related occurrence of higher frequency of somnolence and extrapyramidal symptoms observed in the pediatric population.

The study design and drug exposure in Study 31-03-239 and 31-23-241 have met agency's PWR requirements. No important limitations of data were detected.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

Only one acute controlled study (Study 31-03-239) and one long term open-labeled safety study (Study 31-03-241) were submitted to this sNDA. No data were pooled across studies.

7.4.1.2 Combining data

No combining data were reviewed for this submission.

7.4.2 Explorations for Predictive Factors

No further explorations for predictive factors were conducted in these studies.

7.4.3 Causality Determination

Relationship of an adverse event to treatment was assessed as follows:

Definite: There is a reasonable causal relationship between the study drug and the AE, when the event responds to withdrawal of the study drug (dechallenge), and recurs with rechallenge by administration of the study drug.

Probable: There is a reasonable causal relationship between the study drug and the AE. The event responds to dechallenge. Rechallenge is not required.

Possible: There is a reasonable causal relationship between the study drug and the AE. Dechallenge is lacking or unclear.

Not Likely: There is a temporal relationship to study drug administration, but there is not a reasonable causal relationship between the study drug and the event.

Unrelated: There is not a temporal or causal relationship to the study drug administration.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

Study 31-03-239 is a 6-week, fixed-dose study containing 3 arms—aripiprazole 10 mg, aripiprazole 30 mg, and placebo arms. All study medications were administered orally.

Study 31-03-241 is a 6-month, flexible-dose study. Doses of aripiprazole 2 mg to 30 mg were administered orally on daily basis.

The aripiprazole doses used in these studies are within FDA recommended dose range. There are no specific concerns regarding the study dose regimen.

8.2 Drug-Drug Interactions

The existing label addresses safety outcomes related to potential drug-drug interactions. There have been no new data generated on these topics from this submission.

8.3 Special Populations

See 8.4 Pediatrics.

8.4 Pediatrics

This submission contains three children and adolescents clinical studies—one PK study, one acute efficacy and safety study and one long term open-labeled safety study. The efficacy and safety data from Study 31-03-239 and 31-03-241 are comparable to that obtained from adult schizophrenia clinical trials with the exception of dose-related occurrence of higher frequency of somnolence and extrapyramidal symptoms in adolescent population.

8.5 Advisory Committee Meeting

This submission was not presented to the Psychopharmacologic Drug Advisory Committee.

8.6 Literature Review

A worldwide literature search for published articles pertaining to the safety and efficacy of aripiprazole was conducted. The literature search timeframe includes published articles from March 1, 2005 through a cut-off date of December 1, 2006.

The Literature Reference Search Conducted by Bristol-Myers Squibb
The literature search was conducted by (b) (6).

Search terms:
ARIPIPRAZOLE, ABILITAT, ABILIFY, OPC-14597 (by searching OPC()14597, it also covers OPC 14597), OPC14597, OPC-31 (by searching OPC()31, it also covers OPC 31), OPC31, 129722-12-9 (Chem. Abs. Registry Number), 156680-99-8 (Chem. Abs. Registry Number)

Databases:
MEDLINE, BIOSIS/Biological Abstracts, EMBASE/EMBASE ALERTS, DRUGU/Derwent Drug File, SCISEARCH/Science Citation Index, CAPLUS/Chemical Abstracts, TOXCENTER,

LIFESCI/Life Sciences Collection, IPA/International Pharmaceutical Abstracts, JICST-EPLUS/Japanese Information Center, ADISCTA: Adis Clinical Trials Insight

The literature references were identified by searching above terms in basic index (as opposed to full text) in the above 11 databases. Please note none of the 10 databases are full text, therefore full text searching was not possible.

The Literature Reference Search Conducted by Otsuka Japan
The literature reference search for aripiprazole was conducted at Pharmacovigilance Department of Otsuka Pharmaceutical Company-Japan (Otsuka Japan). Toshinori Kaneyasu is the person in charge of literature search.

In Japan
Search terms:

- ARIPIPRAZOLE
- Terms related to or suggestive of adverse drug reaction, interaction, addiction/intoxication/poisoning/accidents
- Adverse drug reaction: adverse effects caused by medicinal products including over effect of medicinal product, deficiency because it is not included in ingredients of medicinal product e.g. microelement deficiency, abnormal laboratory data etc..
- Interaction: adverse effects from drug-drug interaction, food-drug interaction_e.g. increase or decrease in blood level of medicinal product(s)
- Addiction/Poisoning/intoxication/accidents: adverse effects from improper use including suicide (attempt) or medication error etc.

Database:
SELIMIC—the database established by the external service provider of Otsuka which covers all major medical scientific literature published in Japan.

Outside Japan in Otsuka Territory
Search terms:
ARIPIPRAZOLE

Database:
Major medical and scientific journals published in each country

Conclusion from Literature Search
The literature contains no findings that would adversely affect conclusions about the safety and efficacy of aripiprazole.

8.7 Postmarketing Risk Management Plan

There are no additional recommendations regarding a post-marketing risk management plan.

8.8 Other Relevant Materials

No other relevant materials were provided.

9 OVERALL ASSESSMENT

9.1 Conclusions

Aripiprazole was effective in the acute treatment of adolescent subjects with schizophrenia at daily doses of 10 mg and 30 mg, as demonstrated by statistically significant improvements compared to placebo in PANSS Total Score at Week 6.

Based on safety data from Study 31-03-239 and Study 31-03-241, the safety profile of aripiprazole in adolescents with the diagnosis of schizophrenia is comparable to the adult schizophrenia population, with the exception of dose-related occurrence of higher frequency of somnolence and extrapyramidal symptoms observed in the pediatric population.

9.2 Recommendation on Regulatory Action

Based on the data available at the time of completion of this review, it is recommended that this supplement NDA be granted approvable status.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

There are no further recommendations for risk management activity at this time point.

9.3.2 Required Phase 4 Commitments

There are no further requirements for phase 4 commitments at this time point.

9.3.3 Other Phase 4 Requests

There are no other phase 4 requests.

9.4 Labeling Review

HIGHLIGHTS OF PRESCRIBING INFORMATION

(b) (4)

3 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

9.5 Comments to Applicant

I recommended several changes regarding the proposed labeling. Details can be found in 9.4 Labeling Review.

I also disagree with sponsor's (b) (4) claim. Up to date, the sponsor did not submitted any (b) (4) treatment claim.

Final approval of this sNDA is contingent on mutual agreement on labeling (b) (4)

10 APPENDICES

10.1 Investigators And Study Sites

Table 4-1 Principal Investigators, Study Centers, and Number of Subjects Screened and Enrolled per Center

Study Center Number	Principal Investigator	Study Center Address	Number of Subjects Screened	Number of Subjects Enrolled
001	Paul Ambrosini, MD	Drexel University College of Medicine Department of Psychiatry c/o Friends Hospital 4641 Roosevelt Boulevard Philadelphia, PA 19124 US	0	0
002	J. Robert Batterson, MD	Children's Mercy Hospitals and Clinics 2401 Gillham Road Kansas City, MO 64108 US	1	0
005	Rudy Chavez, MD	Advanced Psychiatric Group 180 North San Gabriel Boulevard Pasadena, CA 91107 US	5	5
006	Robert L. Findling, MD	University Hospitals of Cleveland Division of Child and Adolescent Psychiatry 11100 Euclid Avenue Cleveland, OH 44106-5080 US	4	2
007	Carlos Guerra Jr, MD, PA	9701 Richmond Avenue Suite 200 Houston, TX 77042 US	4	2
008	Sanjay Gupta, MD	Global Research and Consulting 515 Main Street Olean, NY 14760 US	2	0
009	Scott M. Hogan, MD	Pinnacle Point Hospital ATT: Clinical Trials 11501 Financial Center Parkway Little Rock, AR 72211 US	2	1
010	Ali A. Kashfi, MD	597 Maitland Avenue Altamonte Springs, FL 32701 US	2	1

Table 4-1 Principal Investigators, Study Centers, and Number of Subjects Screened and Enrolled per Center

Study Center Number	Principal Investigator	Study Center Address	Number of Subjects Screened	Number of Subjects Enrolled
011	Alain Katic, MD	Claghorn - Lesem Research Clinic 6750 West Loop South Suite 1050 Bellaire, TX 77401 US	2	2
012	Bennett L. Leventhal, MD	Institute for Juvenile Research Department of Psychiatry (M/C 747) University of Illinois at Chicago 1747 W Roosevelt Road, Room 155 Chicago, IL 60608 US	1	0
013	Adam F. Lowy, MD	Comprehensive NeuroScience, Inc Psychiatric Institute of Washington, DC 4228 Wisconsin Avenue, NW Washington, DC 20016 US	4	4
015	Denis Mee-Lee, MD	Hawaii Clinical Research Center 1750 Kalakaua Avenue Suite 2602 Honolulu, HI 96826 US	1	1
016	Marino Molina, Jr, MD	Amedica Research Institute, Inc 625 E 49th Street Hialeah, FL 33013 US	4	1
017	Eliot Moon, MD	Elite Clinical Trials, Inc 34859 Fredrick Street Suite 110 & 111 Wildomar, CA 92595 US	3	2
019	Syed J. Mustafa, MD	Pacific Institute of Medical Sciences 10126 NE 132nd Street Suite C Kirkland, WA 98034 US	5	5
020	Steven G. Potkin, MD	UC Irvine Medical Center 101 The City Drive South Orange, CA 92868 US	1	1

Table 4-1 Principal Investigators, Study Centers, and Number of Subjects Screened and Enrolled per Center

Study Center Number	Principal Investigator	Study Center Address	Number of Subjects Screened	Number of Subjects Enrolled
021	Sohail Punjwani, MD	Professional Clinical Research, Inc c/o Segal Institute for Clinical Research 1065 NE 125th Street Suite 417 North Miami, FL 33161 US	4	1
022	Joachim D. Raese, MD	Behavioral Health 2000, LLC 5945 Brockton Avenue Riverside, CA 92506 US	1	1
023	Rakesh Ranjan, MD	Rakesh Ranjan, MD and Associates, Inc 5010 Mayfield Road Suite 309 Lyndhurst, OH 44124 US	1	1
024	Adelaide S. Robb, MD	Children's National Medical Center 111 Michigan Avenue, NW Washington, DC 20010 US	6	4
025	Russell E. Scheffer, MD	Children's Health System Child & Adolescent Psychiatry and Behavioral Medicine 9000 W Wisconsin Avenue PO Box 1997, MS#750 Milwaukee, WI 53201-1997 US	3	2
026	Michael Schwartz, DO	College Hospital Costa Mesa 301 Victoria Street Costa Mesa, CA 92627 US	0	0
027	Veronique Sebastian, MD	Sooner Clinical Research 5929 N May Avenue Suite 401 Oklahoma City, OK 73112 US	4	3

Table 4-1 Principal Investigators, Study Centers, and Number of Subjects Screened and Enrolled per Center

Study Center Number	Principal Investigator	Study Center Address	Number of Subjects Screened	Number of Subjects Enrolled
029	Raj Shiwach, MD	Insite Clinical Research 2000 N Old Hickory Trail DeSoto, TX 75115 US	2	2
030	Linmarie Sikich, MD	University of North Carolina at Chapel Hill Department of Psychiatry CB #7160 Chapel Hill, NC 27599-7160 US	1	1
031	Juanita Lynn Taylor, MD	University of Arkansas for Medical Sciences College of Medicine 4301 W Markham Little Rock, AR 72205 US	0	0
032	Roger B. Vogelfanger, MD	Compass Intervention Center 7900 Lowrance Road Memphis, TN 38125 US	4	3
033	Kashinath G. Yadalam, MD	Lake Charles Clinical Trials 2770 3rd Avenue Suite 340 Lake Charles, LA 70601 US	2	2
034	James Knutson, MD	Eastside Therapeutic Resource 512 6th Street South Suite 101 Kirkland, WA 98033 US	1	1
035	Juan B. Espinosa, MD	TuKoi Institute for Clinical Research 20820 West Dixie Highway Miami, FL 33180 US	1	1
036	Paul J. Markovitz, MD	Mood and Anxiety Research, Inc 7409 North Cedar Avenue Suite 101 Fresno, CA 93720 US	1	0

Table 4-1 Principal Investigators, Study Centers, and Number of Subjects Screened and Enrolled per Center

Study Center Number	Principal Investigator	Study Center Address	Number of Subjects Screened	Number of Subjects Enrolled
037	Robert L. Hendren, DO	University of California Davis Medical Center MIND Institute 2825 50th Street Sacramento, CA 95817 US	0	0
038	Robert L. Jimenez, MD	Synergy Research, Inc, LLC 7272 Wurzbach Road Suite 1003 San Antonio, TX 78240 US	1	1
039	Willis Holloway Jr, MD	Cutting Edge Research Group 6613 N Meridian Avenue Oklahoma City, OK 73116 US	3	2
040	Anjali A. Pathak, MD	A.P. Psychiatric & Counseling Services 5251 Emerson Street Jacksonville, FL 32207 US	0	0
041	Carlos A. Santana, MD	University of South Florida Department of Psychiatry and Behavioral Medicine 3515 East Fletcher Avenue Tampa, FL 33613 US	1	0
045	Iliyan Ivanov, MD	Mount Sinai School of Medicine 1425 Madison Avenue 6th Floor New York, NY 10029 US	1	1
046	Robert B. DeTrinis, MD	1040 Calhoun Street New Orleans, LA 70118 US	0	0
047	Michael J. Rieser, MD, PSC	2801 Palumbo Drive Suite 202 Lexington, KY 40509 US	4	2

Table 4-1 Principal Investigators, Study Centers, and Number of Subjects Screened and Enrolled per Center

Study Center Number	Principal Investigator	Study Center Address	Number of Subjects Screened	Number of Subjects Enrolled
048	Adly Thebaud, MD	Medical Research Group of Central Florida 2725 Rebecca Lane Suite 107 Orange City, FL 32763 US	6	5
050	Barbara L. Gracious, MD	Department of Psychiatry University of Rochester Medical Center 300 Crittenden Blvd Rochester, NY 14642 US	2	0
051	Poonam Soni, MD	University of Utah School of Medicine Department of Psychiatry 30 North 1900 East Room 5R218 Salt Lake City, UT 84132-2502 US	1	1
053	Ismail B. Sendi, MD, MS	New Oakland Child/Adolsecent and Family Center 42621 Garfield Rd Suite #101 Clinton Township, MI 48038 US	2	2
054	Alan Unis, MD	Sacred Heart Medical Center and Children's Hospital 101 West 8th Avenue Spokane, WA 99204 US	3	2
057	Humberto Quintana, MD	2933 Brakley Avenue, Suite A Baton Rouge, LA 70816-2305 US	3	1
058	James T. Cullinan, DO	314 Smolian Clinic 1700 7th Avenue South University of Alabama at Birmingham Birmingham, AL 35294-0018 US	1	1

Table 4-1 Principal Investigators, Study Centers, and Number of Subjects Screened and Enrolled per Center

Study Center Number	Principal Investigator	Study Center Address	Number of Subjects Screened	Number of Subjects Enrolled
059	Jean A. Frazier, MD	Cambridge Health Alliance Harvard Medical School 1493 Cambridge Street Cambridge, MA 02139 US	0	0
060	Naveed Iqbal, MD	Advanced Bio-Behavioral Sciences, Inc 5 West Main Street Suite 206 Elmsford, NY 10523 US	4	2
063	Sharon E. Cain, MD	University of Kansas Medical Center 3901 Rainbow Boulevard Kansas City, KS 66160 US	0	0
065	Gregory S. Kaczenski, MD	K & S Professional Research Services, LLC 801 Scott Street Little Rock, AK 72201 US	2	2
066	Saul Helfing, MD	Highline-West Seattle Mental Health Center 2600 Southwest Holden Street Seattle, WA 98126 US	0	0
067	Veena Luthra, MD	Clinical Trial Specialists 1 Belmont Avenue Suite 315 Bala Cynwyd, PA 19004 US	1	1
068	Ashraf Attalla, MD	Ridgeview Institute 4015 South Cobb Drive Suite 100 Smyrna, GA 30080 US	4	1
070	Harinder Grewal, MD	Worldwide Research 1908 Sweetwater Road National City, CA 91950 US	4	4

Table 4-1 Principal Investigators, Study Centers, and Number of Subjects Screened and Enrolled per Center

Study Center Number	Principal Investigator	Study Center Address	Number of Subjects Screened	Number of Subjects Enrolled
071	Jeanette Cueva, MD	Bioscience Research, LLC 222 West 14th Street New York, NY 10011 US	1	0
073	Ann C. Childress, MD	Center for Psychiatry and Behavioral Medicine, Inc 7351 Prairie Falcon Road Suite 160 Las Vegas, NV 89128 US	2	2
074	Michel Woodbury Fariña, MD	307 Eleanor Roosevelt St San Juan, PR 00918 US	8	8
075	Gloria M. González-Tejera, MD	RCMI Clinical Research Center University District Hospital 1st Floor University of Puerto Rico Medical Sciences Campus San Juan, PR 00936-5067 US	0	0
078	Joseph A. Kwentus, MD	Precise Clinical Research, Inc Brentwood Plaza Suite 1060 3531 Lakeland Drive Flowood, MS 39232 US	0	0
079	Michael A. Bengtson, MD	University of Florida, Department of Psychiatry 1600 SW Archer Road Gainesville, FL 32610 US	1	1
081	Prof Frederick W. Hickling	The Department of Psychiatry The University Hospital of the West Indies Mona Kingston 7 Jamaica West Indies	6	3

Table 4-1 Principal Investigators, Study Centers, and Number of Subjects Screened and Enrolled per Center

Study Center Number	Principal Investigator	Study Center Address	Number of Subjects Screened	Number of Subjects Enrolled
082	John H. Gilliam, MD	International Clinical Research Associates, LLC 1601 Rolling Hills Drive Suite 201 Richmond, VA 23229 US	3	3
083	Donna J. Scott, MD	Southern Cresent Research 58 Hospital Road Suite 101 Newman, GA 30263 US	1	0
101	Anton Slavchev, MD, PhD	Inpatient Child and Adolescent Psychiatric Clinic Multiprofiled Hospital for Active Treatment "Alexandrovska", 13 "Lunna Paprat" Street 1619 Sofia, Bulgaria	8	8
103	Svetlozar Georgiev, MD	Department of Psychiatry, University Multiprofiled Hospital for Active Treatment "Sveti Georgi" 15A Vassil Aprilov Boulevard 4002 Plovdiv Bulgaria	5	2
104	Stefan Todorov, MD, PhD	Multifunctional Hospital for Active Treatment "St Marina" I Psychiatric Clinical 1 Hristo Smirnenski Street 9010 Varna Bulgaria	12	12
105	Lubomir Jivkov, MD	Regional City Psychiatric Dispensary of Sofia 59 "Ekzarh Jossif" Street 1000 Sofia Bulgaria	0	0

Table 4-1 Principal Investigators, Study Centers, and Number of Subjects Screened and Enrolled per Center

Study Center Number	Principal Investigator	Study Center Address	Number of Subjects Screened	Number of Subjects Enrolled
106	Nadia Polnareva, MD, PhD	Child and Adolescent Psychiatric Clinic "St Nicolas" University Multi-profiled Hospital for Active Treatment "Alexandrovska" 1, G Sofiisky Street 1431 Sofia Bulgaria	0	0
107	Temenuzhka Dechkova-Novakova, MD	District Psychiatric Dispensary - Rousse 20 "Tutrakan" Boulevard 7003 Rousse Bulgaria	4	4
108	Svetlozar Haralanov, MD, PhD	Second Psychiatric Clinic at Specialised Hospital for Active Treatment in Neurology and Psychiatry "Sveti Naum" Tzarigradsko Shausse Blvd IV km 1113 Sofia Bulgaria	3	3
150	Prof Aneta Lakic	Clinic of Neurology and Psychiatry for Children and Adolescents Dr Subotica 6a 11000 Belgrade Serbia and Montenegro	3	2
151	Prof Dr Smijka Popovic Deusic (current) Prof Ivana Timotijevic (original)	Institute of Mental Health, Palmoticeva 37 11000 Belgrade Serbia and Montenegro	5	4
152	Prof Dr Dragan Mitrovic	Institute of Psychiatry Clinical Center Novi Sad Hajduk Veljkova 1 21000 Novi Sad Serbia and Montenegro	6	6
250	Alan L. Schneider, MD	Gateways Hospital and Mental Health Center 1891 Effie Street Los Angeles, CA 90026 US	3	2

Table 4-1 Principal Investigators, Study Centers, and Number of Subjects Screened and Enrolled per Center

Study Center Number	Principal Investigator	Study Center Address	Number of Subjects Screened	Number of Subjects Enrolled
350	Dr Satish Girimaji	National Institute of Mental Health and Neuro Sciences (NIMHANS) Bangalore 560029 India	2	2
351	Dr Deepak Gupta	Center for Child Health Sir Gangaram Hospital Rajinder Nagar New Delhi 110060 India	2	1
352	Dr Shrinivasa Bhat U	KS Hegde Medical Academy, Deralkatte Mangalore 575018 India	1	0
353	Dr Nadukuru Nooka Raju	Government Hospital for Mental Care Chinawaltair Visakhapatnam 530017 India	1	1
354	Dr G. Prasad Rao	Asha Hospital, 298, Road No. 14, Banjara Hills Hyderabad 500034 India	13	12
355	Dr Nilesh Shah	Department of Psychiatry 1st Floor, College Building Lok Manya Tilak Municipal Medical College and Lok Manya Tilak Municipal General Hospital Sion Mumbai 400022 India	0	0
356	Dr Savita Malhotra	Department Psychiatry, Postgraduate Institution of Medical Education and Research Chandighar 160012 India	5	5
357	Dr P. C. Shastri	Dr Shastri's Clinic 3/3 Vivina Co-op Housing Society, SV Road Andheri (West) Mumbai 400058 India	3	3

Table 4-1 Principal Investigators, Study Centers, and Number of Subjects Screened and Enrolled per Center

Study Center Number	Principal Investigator	Study Center Address	Number of Subjects Screened	Number of Subjects Enrolled
358	Dr Ranjive Mahajan	Department of Psychiatry Dayanand Medical College and Hospital Tagore Nagar, Civil Lines Ludhiana 141001 India	5	5
359	Dr T.P. Sudhakar	Department of Psychiatry SV Medical College Tirupati 517507 India	1	1
360	Dr T.S.S. Rao	Department of Psychiatry, JSS Medical College & Hospital, Ramanuja Road Mysore 570004 India	3	3
361	Dr Vihang Vahia	Department of Psychiatry Dr R.N. Cooper General Hospital currently located at V.N. Desai Hospital 11th Road, Santacruze (E) Mumbai 400055 India	0	0
362	Dr Ramanathan Sathianathan	Department of Psychiatry, Madras Medical College & Government Hospital E.V.R. Periyar Salai Chennai, Tamilnadu, 600003 India	5	5
502	José Humberto Nicolini Sánchez, MD	Grupo de Estudios Médicos y Familiares Carracci Carracci 107 Col Insurgentes Extremadura CP 03740 DF México	3	1
504	Rosa Elena Ulloa Flores, MD	Hospital Psiquiátrico Infantil "Dr Juan N. Navarro", Av San Buenaventura 86, Col Belisario Domínguez DF, CP 14080 México	1	1

Table 4-1 Principal Investigators, Study Centers, and Number of Subjects Screened and Enrolled per Center

Study Center Number	Principal Investigator	Study Center Address	Number of Subjects Screened	Number of Subjects Enrolled
505	José Ontiveros Sánchez de la Barquara, MD	INFOSAME Dr Péna No 122, Col Los Doctores, Monterrey, N.L., 64710 Mexico	1	1
507	Severiano Lozano González, MD	Centro Avanzado de Salud Anímica - CASA Padre Mier Poniente 1015, Col Zona Centro Monterrey, Nuevo León, CP 64000 Mexico	1	0
601	Prof Yury A. Alexandrovsky, MD	City Psychiatric Hospital #12 Volokolamskoy shosse 47 123367, Moscow Russia	5	5
603	Prof Leonid M. Bardenstein, MD	Department of Psychiatry, MSUMS, Mental Hospital #15 Moskvorechye Street 7 115522, Moscow Russia	10	9
604	Prof Yuri V. Popov, MD	Bekhterev Research Institute of Psychiatry and Neurology Bekhterev Street 3 193019, Sanct-Petersburg Russia	10	8
605	Prof Elena A. Grigorieva, MD	Yaroslavl Regional Clinical Psychiatry Hospital, Zagorodny Sad Str 6 150003 Yaroslavl Russia	8	8
606	Prof Kausar K. Yakhin, MD	Kazan City Psychoneurological Hospital ul. Volkov 80 420012 Kazan Russia	8	8
608	Prof Alexander O. Bukhanovsky, MD	Scientific Center of Treatment and Rehabilitation "Phoenix", Voroshilovsky pr. 40/128 344010 Rostov-on-Don Russia	5	5

Table 4-1 Principal Investigators, Study Centers, and Number of Subjects Screened and Enrolled per Center

Study Center Number	Principal Investigator	Study Center Address	Number of Subjects Screened	Number of Subjects Enrolled
609	Yuri A. Fessenko, MD, PhD	Child Center of Rehabilitation Treatment "Child Psychiatry", Pesochnaya nab. 4 197376 St-Peterburg Russia	6	4
610	Natalya V. Dobrovolskaya, MD	Center of Psychopathology and Cognitive Disorder City Psycho neurologycal Dispenser N° 10 with Hospital Matveyev pereulok 3 190121 Sanct-Petersburg Russia	5	5
611	Evgenia G. Rebrova, MD	Psychiatry Hospital #3 Fermskoe Shosse 36 197341 Sanct-Peterburg Russia	3	2
612	Prof Valery N. Krasnov, MD	Moscow Research Institute of Psychiatry Poteshnaya street 3 107076 Moscow Russia	5	5
613	Prof Igor V. Boyev, MD	Clinic of Borderline Disorders Stavropol Medical Academy ul Lenina 417 Stavropol, 355038 Russia	7	6
615	Prof Alexander K. Zinkovskiy, MD	Regional Clinical Psychiatry Hopsital N°. 1 named after M.P. Litvinov Burashevo, Kalininsky district Tver Region, 170546 Russia	1	1
650	Dr Victor Marinescu	Spitalul Clinic de Psihiatrie "Dr Alexandru Obregia" Departmentul 9, sos. Berceni nr. 10-12, Sector 4 041914 Bucuresti Romania	0	0

Table 4-1 Principal Investigators, Study Centers, and Number of Subjects Screened and Enrolled per Center

Study Center Number	Principal Investigator	Study Center Address	Number of Subjects Screened	Number of Subjects Enrolled
651	Prof Dr Doina Cosman, MD	Clinica de Psihiatrie nr 3 Spitalul Judetean de Urgenta str. Babes nr. 43 400012 Cluj-Napoca Romania	0	0
652	Prof Dr Aurel Nirestean,	Clinica de psihiatrie nr 2, Spitalul Judetean de Urgenta str Gheorghe Marinescu nr. 38 540139 Tirgu Mures Romania	2	2
653	Prof Dr Iuliana Dobrescu	Spitalul Clinica de Psihiatrie "Dr Alexandru Obregia" Clinica de Psihiatrie a Copilului si adolescenti, Sos Berceni nr. 10-12 sector 4 041914 Bucuresti Romania	9	8
654	Dr Bogdan Pacala	Spitalul Clinic de Psihiatrie "Dr Gheorghe Preda" str. Bagdazar nr. 12 550082 Sibiu Romania	0	0
701	Alberto Manuel Bertoldi	Clínica Privada San Agustín Calle 55 N° 763 La Plata Buenos Aires Argentina C.P. 1900	5	5
703	Gustavo Martin Petracca	Instituto Neurociencias Buenos Aires (INEBA) Guardia vieja 4435, C1192AAW Ciudad Autonoma de Buenos Aires Argentina	0	0
704	Carlos Alberto Morra	Sanatorio Morra, Av Sagrada Familia y Nazareth, Barrio Urca Córdoba (5009) Argentina	2	1
705	Roxana Beatriz Galeno	Instituto Neurociencias, Olegario V. Andrade N° 290 Ciudad de Mendoza, Mendoza Argentina (5500)	5	5

Table 4-1 Principal Investigators, Study Centers, and Number of Subjects Screened and Enrolled per Center

Study Center Number	Principal Investigator	Study Center Address	Number of Subjects Screened	Number of Subjects Enrolled
707	Rolando Dante Salinas	SYTIUM Beruti 2522 P6 (C1425) Capital-Federal, Buenos Aires Argentina	1	1
709	Ricardo Marcelo Corral	Centro de Neuropsiquiatría Marcelo T de Alvear 2430 5° A, (C1122AAN), Buenos Aries Argentina	2	2
710	Julio José Herrera	Centro de Psiquiatría Biológica Pedro Molina 249 1° piso Oficina 2, Ciudad de Mendoza, Mendoza (5500) Argentina	1	1
711	Miguel Márquez, MD	CRF Investigaciones Clínicas Juncal 802 2 "F" Ciudad Autónoma de Buenos Aires Argentina (C1062ABF)	1	0
750	Prof Soo-Churl, Cho	Division of Child and Adolescent Psychiatry Seoul National University Hospital 28 Yeongun-dong, Jongno-gu Seoul, South Korea 110-744	0	0
754	Prof Jae-Min, Kim	Department of Psychiatry, Chonnam National University Hospital 8 Hak-dong, Dong-gu Gwang-ju, South Korea 501-757	1	1
755	Associate Prof Sung-Hoon, Jeong	Department of Psychiatry, Kyungpook National University Hospital 50 Samdeok-2ga Dae-gu, South Korea 700-721	0	0
756	Associate Prof Jeong-Seop, Lee	Department of Pyschiatry Inha University Hospital 7-206, 3-ga, Shinheung-dong Jung-gu Incheon, South Korea 400-711	2	1

Table 4-1 Principal Investigators, Study Centers, and Number of Subjects Screened and Enrolled per Center

Study Center Number	Principal Investigator	Study Center Address	Number of Subjects Screened	Number of Subjects Enrolled
757	Associate Prof Dong-Ho, Song	Department of Psychiatry Yongdong Sevrance Hospital 146-92, Dogok-dong Kangnam-gu Seoul, South Korea 135-720	0	0
758	Prof Keun-Ah, Cheon	Department of Psychiatry, Kwandong University MyungJi Hospital 2Fr. 697-24, Hwajung-dong Koyang-si Kyunggi-do, South Korea 412-270	0	0
759	Assistant Prof Ji-Hoon, Kim	Department of Psychiatry, 2F Pusan National University Hospital 1-10 Ami-Dong, Seo-gu Pusan, South Korea 602-791	2	2
802	Prof Dr SC. Goran Dodig, MD	Clinical Hospital Split Psychiatric Clinic Spinčićeva 1 21000 Split Croatia	2	2
803	Pavo Filakovic, MD, PhD	Psychiatric Clinic Clinical Hospital Osijek 31000 Osijek, Huttlerova 4 Croatia	3	3
805	Dubravka Kocijan-Hercigonja, MD, PhD	Polyclinic for Neurology and Psychiatry 10000 Zagreb, Kranjceviceva 8 Croatia	2	2
806	Prof Dr Tanja Franciskovic (current) Ljiljana Moro (original)	KBC Rijeka Clinic for Psychiatry Cambierieva 17/7, 51000 Rijeka Croatia	2	2

Table 4-1 Principal Investigators, Study Centers, and Number of Subjects Screened and Enrolled per Center

Study Center Number	Principal Investigator	Study Center Address	Number of Subjects Screened	Number of Subjects Enrolled
807	Neven Henigsberg	Poliklinika Neuron Croatian Institute for Brain Research, University of Zagreb Medical School, University of Zagreb Salata 12, 10000 Zagreb Croatia	1	0
841	Professor G.A.D. Hart	Room 202 Sandton Medical Center North Block 3 Main Road, Bryanston 2021 South Africa	0	0
842	Dr Prema R. Laban	Crompton Medical Centre West Crompton Street Pinetown 3610 South Africa	2	2
843	Dr L. Nel	Dey Clinic 345 Dey Street Nieuw Muckleneuk 0181 South Africa	3	3
844	Professor C.A. Gagiano	Westdene Research Center 32 Pres. Steyn Avenue Westdene Bloemfontein 9301 South Africa	0	0
845	Dr C.F. Weyers	Calmdene Research Unit 1 Haarburger Crescent Westdene Bloemfontein 9301 South Africa	0	0
850	Prof Valeriy N. Kuznetsov, MD, PhD	Kiev Medical Academy of Postgraduate Education Dept of Psychiatry Psychiatric Hospital No.1 103-A Frunze Str 04080 Kiev Ukraine	4	4

Table 4-1 Principal Investigators, Study Centers, and Number of Subjects Screened and Enrolled per Center

Study Center Number	Principal Investigator	Study Center Address	Number of Subjects Screened	Number of Subjects Enrolled
851	Prof Oleg Sosontovich Chaban, MD, PhD	Neuroses and Somatoform Disorders Clinic, Ukrainian Research Institute of Social, Forensic Psychiatry and Drug Abuse 1st Road Hospital 8A M.Kotsubinskogo Str Kiev, 03049 Ukraine	4	4
855	Prof Kazakova Svitlana Yevgenivna, MD, PhD	Lugansk Regional Clinical Psychoneurological Hospital, Department of Psychiatry of Lugansk State Medical University 22, 50 let Oborony Luganska, Lugansk, 91045 Ukraine	3	3
856	Prof Valeriy Bitenskyy	Psychiatry Department Odessa State Medical University 9 Acad. Vorobjova Str Odessa 65006 Ukraine	1	1
858	Prof Pidkorytov Valeriy S., MD PhD	Department of Clinical, Social and Child Psychiatry Institute of Neurology, Psychiatry and Narcology AMS of Ukraine 46 Acad. Pavlova Str Kharkiv 61068 Ukraine	2	2
859	Dr Svitlana M. Moroz, PhD	Psychosomatic Center of Dnipropetrovsk Regional Clinical Hospital Oktyabrska sq,14 Dnepropetrovsk 49616 Ukraine	1	1
913	Michael Plopper, MD	Sharp Mesa Vista Hospital 7850 Vista Hill Avenue San Diego, CA 92123 US	1	0

930	David Howard Flaherty, DO	Fidelity Clinical Research, Inc c/o Segal Institute for Clinical Research 7481 W Oakland Park Blvd, Suite 100 Ft Lauderdale, FL 33319 US	1	0

10.2 Appendix To Integrated Review of Efficacy

Table 26 Mean Change from Baseline in PANSS Total Score by Week (OC)

	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6	
TREATMENT GROUP	N	MEAN	N	LSMEAN[1]	N	LSMEAN[1]	N	LSMEAN[1]	N	LSMEAN[1]	N	LSMEAN[1]	N	LSMEAN[1]
ARIP-10MG	99	93.7	98	-6.9	97	-14.0	88	-20.1	87	-24.0	86	-27.6	84	-30.6
ARIP-30MG	97	94.9	95	-10.4	93	-15.7	90	-23.4	85	-26.4	84	-30.4	84	-31.9
PLACEBO	98	95.0	97	-7.2	95	-12.3	93	-17.9	91	-19.3	88	-21.7	90	-22.3

2-SIDED P-VALUES[2] FOR PAIRWISE COMPARISONS WITH PLACEBO

ARIP-10MG VS PLACEBO	0.5375	0.8390	0.4001	0.3528	0.0347	0.0124	0.0011
ARIP-30MG VS PLACEBO	0.9372	0.0465	0.1108	0.0200	0.0016	0.0003	0.0002

REFERENCES

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/s/

Jing Zhang
9/14/2007 10:05:09 AM
MEDICAL OFFICER

Mitchell Mathis
9/14/2007 01:10:25 PM
MEDICAL OFFICER
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-436/S017

21-713/S012

21-729/S004

21-866/S004

STATISTICAL REVIEW(S)

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

STATISTICAL REVIEW AND EVALUATION

Clinical Studies

NDA/Serial Number:	21-436/S017
Drug Name:	Abilify® (Aripiprazole)
Indication:	Treatment of Adolescent Patients with Schizophrenia
Applicant:	Otsuka Pharmaceutical
Dates:	Date of Document: 03/23/2007
	PDUFA Due Date: 09/27/2007
Review Priority:	Priority
Biometrics Division:	Biometrics I, HFD-710
Statistical Reviewer:	Yeh-Fong Chen, Ph.D.
Concurring Reviewers:	Peiling Yang, Ph.D.
	Kooros Mahjoob, Ph.D.
Medical Division:	Division of Psychiatry Products, HFD-130
Clinical Team:	Clinical Reviewer: Jing Zhang, M.D.
	Clinical Team Leader: Mitchell Mathis, M.D. (Deputy Director and also Acting Team Leader)
Project Manager:	Keith Kiedrow, Pharm. D., LCDR USPHS

Table of Contents

1. EXECUTIVE SUMMARY

1.1 CONCLUSIONS AND RECOMMENDATIONS

The only submitted efficacy study 31-03-239 is determined to be a positive study, **which demonstrated the aripiprazole's** efficacy (both 10 mg/day and 30 mg/day) for the treatment of adolescent schizophrenia. Now that 10 mg/day of aripiprazole had shown statistically significant efficacy, (b) (4)

1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

The sponsor submitted Study 31-03-239 as part of the Abilify™ (aripiprazole) **pediatric efficacy program designed to address the FDA's Written Request to** systematically study the safety and efficacy of aripiprazole in adolescents aged 13 to 17 years with schizophrenia. This study tested the safety and efficacy of aripiprazole tablets 10 mg/day and 30/day compared to placebo in adolescent patients with **schizophrenia. Based on the sponsor's** analysis results for the primary endpoint, change from baseline to Week 6 (LOCF data) in the PANSS Total Score, they concluded that aripiprazole was effective in the treatment of adolescent subjects with schizophrenia at daily doses of 10 mg and 30 mg (b) (4)

1.3 STATISTICAL ISSUES AND FINDINGS

This reviewer confirmed the sponsor's analysis results for the primary and secondary endpoints for Study 31-03-239. It was agreed **that the aripiprazole's efficacy at both** 10 mg/day and 30 mg/day for adolescent schizophrenia patients was demonstrated based on this only efficacy study (b) (4)

Now that the 10 mg/day of aripiprazole had already been shown to have statistically significant efficacy in comparison with placebo as a treatment of adolescent schizophrenia, (b) (4)

2. INTRODUCTION

This study was conducted in Argentina, Bulgaria, Croatia, India, Jamaica, Mexico, Romania, Russia, Serbia, South Africa, South Korea, Ukraine, and the US in approximately 300 subjects at 141 study centers.

2.1 OVERVIEW

Abilify® (aripiprazole, OPC-14597, BMS-337039) is approved in the United States of America for the treatment of adults with acute schizophrenia (as of November 2002), maintenance of stability in schizophrenia (as of August 2003), treatment of acute manic and mixed episodes of bipolar disorder (as of September 2004), and for the maintenance of efficacy in bipolar I disorder (as of March 2005). In response to the **FDA's Pediatric Written Request (PWR)** (dated February 11, 2003), the sponsor designed the aripiprazole pediatric efficacy program (APEX) to provide controlled clinical data regarding the use of aripiprazole for the treatment of schizophrenia in the adolescent population and mania associated with bipolar disorder in the child and adolescent population. The APEX program included four studies: one safety, tolerability and pharmacokinetic (PK) study (31-03-238), one randomized, double-blind, placebo-controlled safety and efficacy study each in schizophrenia subjects and bipolar mania subjects (Studies 31-03-239 and 31-03-240), and a roll-over, open-label safety study for subjects who complete either of the double-blind trials (31-03-241).

The efficacy study included in this NDA submission is Study 31-03-239 for the adolescent subjects (aged 13 to 17 years) with schizophrenia. Based on the study results, the sponsor concluded that aripiprazole was effective at daily doses of 10 mg and 30 mg. The primary efficacy measure used in the trial was the mean change from Baseline to Endpoint (Day 42) in the Positive and Negative Syndrome Scale (PANSS) Total Score.

2.2 DATA SOURCES

This NDA submission including the data and study report are stored in the EDR of CDER with the following link: \\CDSESUB1\N21436\S_017\2007-03-23.

3. STATISTICAL EVALUATION

3.1 EVALUATION OF EFFICACY

3.1.1 Description of Study 31-03-239

This section of study description is based on the clinical study report (CSR) in the NDA submission. Any major discrepancy between this CSR and the study protocol **will be discussed in the section of the statistical reviewer's findings and comments.**

3.1.1.1 Study Objectives

The primary objective of this study was to determine the safety and efficacy of aripiprazole tablets administered as 10 mg QD and 30 mg QD in adolescent subjects, 13 to 17 years of age, with a DSM-IV diagnosis of schizophrenia. This study was **designed in response to the FDA's PWR.**

3.1.1.2 Study Design

This study was a multi-center, randomized, double-blind, placebo-controlled trial designed to assess the safety and efficacy of two fixed doses of aripiprazole (10 mg and 30 mg) compared to placebo in adolescent subjects, 13 to 17 years of age (inclusive), with a DSM-IV diagnosis of schizophrenia. The DSM-IV diagnosis was confirmed by administering the Schedule for Affective Disorders and Schizophrenia for School Aged Children: Present and Lifetime Version (K-SADS-PL) semi-structured interview of patients and parents/caregivers by an adequately trained clinician. Confirmation of the DSM-IV diagnosis of schizophrenia using a valid and reliable semi-structured interview was required in the PWR. These procedures could have been completed over multiple clinic visits if necessary.

The study was conducted on an outpatient basis (with the option for inpatient hospitalization, if needed), and in a partial or full inpatient setting at any given time in the study. A minimum of 350 subjects at approximately 141 sites globally were anticipated to be screened with the expectation that approximately 300 subjects would be randomized to yield at least 255 evaluable subjects (85 per treatment arm). Subjects participated in this study for up to 10 weeks, including a 28-day screening period, and a 42-day treatment period. Eligible subjects who completed this study had the option to enroll into an open-label safety study of aripiprazole (Study 31-03-241) for an additional 6 months.

After a minimum 3-day antipsychotic washout period, only subjects who continued to meet entrance criteria (PANSS≥70) at the baseline visit (Day 1) were evenly randomized to receive a double-blind medication as follows:

- Arm 1 (10 mg treatment arm): Aripiprazole 2 mg QD for 2 days, aripiprazole 5 mg QD for 2 days, and aripiprazole 10 mg QD as the target dose, starting on Day 5.
- Arm 2 (30 mg treatment arm): Aripiprzole 2 mg QD for 2 days, aripiprazole 5 mg AD for 2 days, aripiprazole 10 mg QD for 2 days, aripiprazole 15 mg AD for 2 days, aripiprazole 20 mg QD for 2 days, aripiprazole 30 mg QD as the target dose, starting on Day 11.
- Arm 3 (placebo arm): Matching placebo for aripiprazole tablets.

3.1.1.3 Efficacy Variables and Analyses

Efficacy Variables

The primary efficacy measure was the mean change from baseline to endpoint (Day 42) in the Positive and Negative Syndrome Scale (PANSS) Total Score. Secondary efficacy measures include mean changes in scores from baseline to endpoint (Day 42) **in the Children's Global Assessment Scale (CGAS), CGI-Severity, CGI-Improvement,** and PANSS Positive and PANSS Negative Subscales; and time to discontinuation due to all reasons.

Efficacy Analyses

The null hypothesis for the primary efficacy analysis in this study is that there is no difference between either of the two aripiprazole treatment groups and the placebo control group based on change from baseline in the PANSS Total Score. The primary efficacy endpoint was the change from baseline in PANSS Total Score at Day 42 (Week 6) in the LOCF data set. The primary statistical comparisons were aripiprazole 10-mg target dose versus placebo, and aripiprazole 30-mg target dose versus placebo. All randomized subjects who had both baseline and post-baseline PANSS Total Score were included in the primary efficacy analysis.

Descriptive statistics for PANSS Total Scores and change from baseline scores were presented by treatment group for each visit. The change from baseline scores (LOCF) were analyzed using an analysis of covariance (ANCOVA) model with treatment and region as factors, and baseline PANSS Total Score as covariate. The treatment by region interaction term was investigated. For the baseline PANSS Total Score, only treatment and region were included in the analysis of variance (ANOVA) model. The least squares (LS) means obtained from the type III analysis using Statistical Analysis System were used for the treatment comparisons. Two-tailed student's t-tests were used to test the difference between LS means within the ANCOVA or ANOVA model.

A nominal overall significance level of 0.05 (two-tailed) was used in testing statistical significance of these two comparisons. In order to account for multiplicity in testing the two comparisons, the following Hochberg's procedure was used: if both p-values were less than 0.05 (two-tailed), statistical significance was declared for both doses. If the larger of the two p-values was greater than 0.05, the smaller p-value was compared with 0.025 (two-tailed) and the corresponding treatment comparison was declared statistically significant if this p-value was less than 0.025.

In addition to the primary analysis of the PANSS Total Score at Week 6, analyses of changes from baseline in PANSS Total Scores were performed as secondary analyses at all scheduled visits for both LOCF and OC data sets.

3.1.2 Efficacy Results of Study 31-03-239

3.1.2.1 Disposition of Patients and Baseline Characteristics

The subject disposition was summarized in Table 1. Of the 302 subjects enrolled, all were analyzed for efficacy and safety. Demographic characteristics are summarized in Table 2. The three treatment arms were demographically similar and had similar baseline disease characteristics. The majority of subjects were male (56.6%), Caucasian (60.0%), and non-Hispanic (86.0%). The mean age was 15.5 years (range, 13.0 to 17.0 years).

Table 1 Subject Disposition for Study 31-03-239

	ARIP-10 mg	ARIP-30 mg	Placebo	Total
Screened				371
Randomized	100 (100)	102 (100)	100 (100)	302 (100)
Dosed/Analyzed for Safety	100 (100)	102 (100)	100 (100)	302 (100)
Completed	84 (84.0)	84 (82.4)	90 (90.0)	258 (85.4)
Discontinued	16 (16.0)	18 (17.6)	10 (10.0)	44 (14.6)
Adverse event	7 (7.0)	4 (3.9)	2 (2.0)	13 (4.3)
Lost to follow up	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.3)
Subject withdrew consent	4 (4.0)	12 (11.8)	5 (5.0)	21 (7.0)
Protocol deviation	0 (0.0)	1 (1.0)	1 (1.0)	2 (0.7)
Lack of efficacy as determined by the investigator	5 (5.0)	1 (1.0)	1 (1.0)	7 (2.3)
Analyzed for Efficacy	100 (100)	102 (100)	100 (100)	302 (100)

Source: Sponsor's Table 8.1-1 of Clinical Study Report

Table 2 Demographic Characteristics for All Randomized Subjects for Study 31-03-239

Characteristic	Statistic	Aripiprazole 10 mg (N = 100)	Aripiprazole 30 mg (N = 102)	Placebo (N=100)	Total (N=302)
Age (years)	N	100	102	100	302
	Mean (SD)	15.6 (1.3)	15.4 (1.4)	15.4 (1.4)	15.5 (1.4)
	Range	13-17	13-17	13-17	13-17
Height (cm)	N	100	102	100	302
	Mean (SD)	164.0 (10.8)	167.1 (11.4)	166.0 (10.0)	165.7 (10.8)
	Range	139.0-191.0	140.8-196.5	141.0-198.0	139.0-198.0
Weight (kg)	N	100	102	100	302
	Mean (SD)	63.5 (19.1)	64.5 (16.0)	63.4 (15.6)	63.8 (16.9)
	Range	30.0-131.0	36.0-124.5	36.7-108.0	30.0-131.0
BMI	N	100	102	100	302
	Mean (SD)	23.5 (6.0)	23.0 (4.9)	22.9 (5.3)	23.1 (5.4)
	Range	13.6-51.1	16.1-43.0	15.3-40.3	13.6-51.1
Gender	Male, n (%)	45 (45.0)	65 (63.7)	61 (61.0)	171 (56.6)
	Female, n (%)	55 (55.0)	37 (36.3)	39 (39.0)	131 (43.4)
Race	Caucasian, n (%)	54 (54.0)	62 (61.0)	64 (64.0)	180 (60.0)
	Black, n (%)	17 (17.0)	11 (11.0)	6 (6.0)	34 (11.0)
	American Indian or Alaskan Native, n (%)	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.3)
	Asian, n (%)	16 (16.0)	12 (12.0)	15 (15.0)	43 (14.0)
	Other, n (%)	13 (13.0)	17 (17.0)	14 (14.0)	44 (15.0)
Ethnicity	Hispanic/Latino, n (%)	12 (12.0)	15 (15.0)	14 (14.0)	41 (14.0)
	NonHispanic/Latino, n (%)	88 (88.0)	87 (85.0)	86 (86.0)	261 (86.0)

Source: Sponsor's Table 8.2-1 of Clinical Study Report

3.1.2.2 Sponsor's Efficacy Analysis Results

Primary Endpoint

The sponsor's analysis results for the mean change from baseline in PANSS Total Score by week are presented in the following Table 3. As shown in the table, aripiprazole 10 mg and 30 mg showed statistically significant improvements over placebo in the PANSS Total Score at Week 6. Using the LOCF data set, the PANSS Total Scores at Week 6 were -26.7 in the aripiprazole 10 mg arm, -28.6 in the aripiprazole 30 mg arm, and -21.2 in the placebo arm. The comparison between aripiprazole and placebo was significant at both doses (p=0.0414 for aripirpazole 10 mg versus placebo and p=0.0061 for aripiprazole 30 mg versus placebo).

Using the OC data set, the PANSS Total Score at Week 6 were -30.6 in the aripiprazole 10 mg arm, -31.9 in the aripiprazole 30 mg arm, and -22.3 in the placebo arm. The comparison between aripiprazole and placebo was significant at both doses (p = 0.0011 for ariprazole 10 mg versus placebo and p = 0.0002 for aripiprazole 30 mg versus placebo). The detailed weekly OC analysis results are shown in Table 6.1 of Appendix.

Table 3 Sponsor's Analysis Results for Mean Change from Baseline in Positive and Negative Syndrome Scale (PANSS) Total Score by Week (LOCF) for Study 31-03-239

Visit/Week	Arip 10 mg		Arip 30 mg		Placebo		P-value Arip10 mg vs. Placebo	P-value Arip 30 mg vs. Placebo
	N	Mean*	N	Mean*	N	Mean*		
Baseline	99	93.7	97	94.9	98	95.0	0.5375	0.9372
Week 1	98	-6.9	95	-10.4	97	-7.2	0.8390	0.0465
Week 2	99	-13.9	97	-15.2	98	-12.5	0.4748	0.1828
Week 3	99	-18.4	97	-22.1	98	-16.7	0.4759	0.0269
Week 4	99	-21.8	97	-24.6	98	-19.0	0.2346	0.0181
Week 5	99	-24.5	97	-27.3	98	-20.3	0.0979	0.0057
Week 6	99	-26.7	97	-28.6	98	-21.2	0.0414	0.0061

* The reported means are least square means adjusted from an ANCOVA model of change from baseline, with baseline as a covariate and terms for treatment and region strata.
Source: Sponsor's Table 9.3.1-1 of Clinical Study Report

Reviewer's Note: There were 8 patients who were randomized but did not have any post randomization PANSS Total Score, so only total 294 patients were included in the primary analysis results.

Secondary Endpoints

Table 4 summarized the sponsor's analysis results for CGAS Score, CGI-Severity Score, CGI Improvement Score, PANSS Positive Subscale Score, PANSS Negative Subscale Score. Regarding the time to discontinuation for all reasons variable, the sponsor showed a Kaplan-Meier product limit plot and concluded that no statistically significant differences were observed between the aripiprazole 10 mg arm and placebo or the aripiprazole 30 mg arm and placebo.

Table 4 Summary of Sponsor's Analysis Results for Secondary Endpoints

Visit/Week	Arip 10 mg		Arip 30 mg		Placebo		P-value Arip10 mg vs. Placebo	P-value Arip 30 mg vs. Placebo
	N	Mean*	N	Mean*	N	Mean*		
Mean Change from Baseline to Week 6 in CGAS Score (LOCF)								
Baseline	97	46.7	94	45.6	98	45.4	0.4278	0.8667
Week 6	97	14.7	94	14.8	98	9.8	0.0054	0.0044
Mean Change from Baseline to Week 6 in CGI Severity Score (LOCF)								
Baseline	99	4.5	97	4.6	98	4.6	0.2381	0.5990
Week 6	99	-1.2	97	-1.3	98	-0.9	0.0071	0.0016
Mean CGI Improvement Score (LOCF)								
Week 6	99	2.7	97	2.5	98	3.1	0.0167	0.0004
Mean Change from Baseline to Week 6 in PANSS Positive Subscale Score (LOCF)								
Baseline	99	22.1	97	23.5	98	22.9	0.2548	0.4602
Week 6	99	-7.6	97	-8.1	98	-5.6	0.0134	0.0018
Mean Change from Baseline to Week 6 in PANSS Negative Subscale Score (LOCF)								
Baseline	99	25.4	97	24.9	98	25.6	0.7881	0.3984
Week 6	99	-6.9	97	-6.6	98	-5.4	0.0462	0.0972

Source: Sponsor's Tables 9.4.2-1 to 9.4.6-1 of Clinical Study Report

3.1.2.3 Reviewer's Findings and Comments

This reviewer confirmed the sponsor's analysis results for the primary and secondary endpoints for Study 31-03-239. It was agreed that the aripiprazole's efficacy at both 10 mg/day and 30 mg/day for adolescent schizophrenia patients was demonstrated based on this only efficacy study. This reviewer also noted that the sponsor claimed (b) (4) Now that the 10 mg/day of aripiprazole had already shown statistically significant efficacy in comparison with placebo as a treatment of adolescent schizophrenia, (b) (4)

3.2 EVALUATION OF SAFETY

Please refer to the medical review for the evaluation of safety.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

For the primary endpoint, the sponsor performed the subgroup analyses for region, gender, and race for Study 31-03-239. Since this study was only the aripiprazole's efficacy in the treatment of adolescent patients, which were aged from 13 to 17 years, no age subgroup analysis was performed. This reviewer confirmed the sponsor's analysis results. For exploratory purpose, this reviewer also performed the ANCOVA analyses by including the factor of treatment and a covariate of baseline PANSS Total scores.

4.1 GENDER, RACE AND AGE

The sponsor's subgroup analyses for gender and race are shown in Tables 5 and 6. Except the comparisons between aripiprazole 30 mg and placebo for male and for white patients, all other comparisons had nominal p-values >0.05. Since these subgroup analyses are only for the exploratory purpose, the p-values should be interpreted with caution.

Table 5 Sponsor's Gender Subgroup Analysis Results for Change from Baseline to End Visit of PANSS Total Score (by LOCF Data) for Study 31-03-239

Treatment	Visit	Mean (SD)	Change from Baseline to Last Visit Mean (SD)
Male			
Arip-10 mg (N=44)	Baseline	94.5 (14.3)	-27.1 (19.0)
	Last Visit (Week 6)	67.4 (20.6)	
Arip-30 mg (N=61)	Baseline	95.0 (13.5)	-27.9 (20.2)*
	Last Visit (Week 6)	67.0 (19.5)	
Placebo (N=59)	Baseline	94.6 (16.7)	-20.2 (19.3)
	Last Visit (Week 6)	74.4 (22.2)	
Female			
Arip-10 mg (N=55)	Baseline	93.1 (16.9)	-24.1 (21.4)
	Last Visit (Week 6)	69.0 (25.0)	
Arip-30 mg (N=36)	Baseline	94.9 (18.6)	-27.5 (20.0)
	Last Visit (Week 6)	67.4 (25.3)	
Placebo (N=39)	Baseline	95.6 (13.5)	-20.2 (16.5)
	Last Visit (Week 6)	75.4 (17.8)	

*: 0.01<p-value<0.05 by the ANCOVA model with treatment and baseline.
Source: Sponsor's Table STAT-1.1.1.3

Table 6 Sponsor's Race Subgroup Analysis Results for Change from Baseline to End Visit of PANSS Total Score (by LOCF Data) for Study 31-03-239

Treatment	Visit	Mean (SD)	Change from Baseline to Last Visit Mean (SD)
White			
Arip-10 mg (N=53)	Baseline	92.3 (16.4)	-21.5 (19.7)
	Last Visit (Week 6)	70.8 (21.5)	
Arip-30 mg (N=59)	Baseline	92.2 (14.2)	-24.2 (21.0)*
	Last Visit (Week 6)	68.0 (20.2)	
Placebo (N=64)	Baseline	92.2 (13.2)	-17.0 (16.8)
	Last Visit (Week 6)	75.1 (17.9)	
Black or African American			
Arip-10 mg (N=17)	Baseline	95.6 (17.8)	-32.8 (20.3)
	Last Visit (Week 6)	62.8 (22.8)	
Arip-30 mg (N=11)	Baseline	105.6 (13.4)	-24.2 (12.9)
	Last Visit (Week 6)	81.5 (19.9)	
Placebo (N=6)	Baseline	98.5 (16.7)	-35.3 (26.0)
	Last Visit (Week 6)	63.2 (23.8)	

Treatment	Visit	Mean (SD)	Change from Baseline to Last Visit Mean (SD)
American Indian or Alaska Native			
Placebo (N=1)	Baseline	98.0	-17.0
	Last Visit (Week 6)	81.0	
Asian			
Arip-10 mg (N=16)	Baseline	91.3 (11.5)	-23.1 (21.0)
	Last Visit (Week 6)	68.2 (29.3)	
Arip-30 mg (N=12)	Baseline	90.3 (11.0)	-39.3 (15.7)
	Last Visit (Week 6)	51.1 (13.8)	
Placebo (N=13)	Baseline	97.2 (15.8)	-25.2 (19.1)
	Last Visit (Week 6)	72.1 (22.4)	
Other			
Arip-10 mg (N=13)	Baseline	99.8 (14.4)	-34.7 (18.9)
	Last Visit (Week 6)	65.2 (22.6)	
Arip-30 mg (N=15)	Baseline	101.5 (20.3)	-35.2 (19.6)
	Last Visit (Week 6)	66.3 (26.7)	
Placebo (N=14)	Baseline	104.1 (21.6)	-23.6 (17.2)
	Last Visit (Week 6)	80.5 (28.1)	

*: 0.01<p-value<0.05 by the ANCOVA model with treatment and baseline.
Source: Sponsor's Table STAT-1.1.1.4

4.2 OTHER SPECIAL/SUBGROUP POPULATIONS

Table 7 shows the sponsor's results of subgroup analysis by region. This reviewer found that all comparisons between aripiprazole (15 mg or 30 mg) and placebo had nominal p-values >0.05.

Table 7 Sponsor's Region Subgroup Analysis Results for Change from Baseline to End Visit of PANSS Total Score (by LOCF Data) for Study 31-03-239

Treatment	Visit	Mean (SD)	Change from Baseline to Last Visit Mean (SD)
US			
Arip-10 mg (N=31)	Baseline	97.2 (16.5)	-31.4 (22.5)
	Last Visit (Week 6)	65.8 (21.8)	
Arip-30 mg (N=31)	Baseline	101.3 (15.1)	-30.7 (21.4)
	Last Visit (Week 6)	70.5 (24.1)	
Placebo (N=31)	Baseline	98.6 (17.0)	-23.7 (20.9)
	Last Visit (Week 6)	74.9 (26.8)	
Europe			
Arip-10 mg (N=17)	Baseline	92.2 (16.1)	-21.8 (19.3)
	Last Visit (Week 6)	70.4 (22.1)	
Arip-30 mg (N=11)	Baseline	88.5 (11.9)	-21.2 (16.2)
	Last Visit (Week 6)	67.3 (16.6)	
Placebo (N=6)	Baseline	91.9 (12.7)	-15.8 (16.1)
	Last Visit (Week 6)	76.1 (15.4)	

Treatment	Visit	Mean (SD)	Change from Baseline to Last Visit Mean (SD)
Other Regions			
Arip-10 mg (N=17)	Baseline	92.0 (13.7)	-24.6 (18.1)
	Last Visit (Week 6)	67.4 (27.2)	
Arip-30 mg (N=11)	Baseline	99.0 (17.9)	-36.7 (21.5)
	Last Visit (Week 6)	62.4 (26.8)	
Placebo (N=6)	Baseline	96.7 (18.1)	-25.1 (16.4)
	Last Visit (Week 6)	71.6 (20.5)	

Source: Sponsor's Table STAT-1.1.1.2

5. SUMMARY AND CONCLUSIONS

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

This reviewer confirmed the sponsor's analysis results for the primary and secondary endpoints for Study 31-03-239. It was agreed that the aripiprazole's efficacy at both 10 mg/day and 30 mg/day for adolescent schizophrenia patients was demonstrated based on this only efficacy study (b) (4)

5.2 CONCLUSIONS AND RECOMMENDATIONS

The only submitted efficacy study 31-03-239 is determined to be a positive study, which demonstrated the aripiprazole's efficacy (both 10 mg/day and 30 mg/day) for the treatment of adolescent schizophrenia. Now that 10 mg/day of aripiprazole had shown statistically significant efficacy, (b) (4)

Yeh-Fong Chen, Ph.D.
Mathematical Statistician

cc: NDA 21-436 (S17)
HFD-130/Dr. Laughren
HFD-130/Dr. Mathis
HFD-130/Dr. Zhang
HFD-130/Mr. Kiedrow
HFD-700/Dr. Nevius
HFD-700/Ms. Patrician
HFD-710/Dr. Mahjoob
HFD-710/Dr. Hung
HFD-710/Dr. Yang

6. APPENDICES

Table 6.1 Sponsor's OC analysis Results for PANSS Total Score for Study 31-03-239

Visit/Week	Arip 10 mg		Arip 30 mg		Placebo		P-value Arip10 mg v.s. Placebo	P-value Arip 30 mg v.s. Placebo
	N	Mean*	N	Mean*	N	Mean*		
Baseline	99	93.7	97	94.9	98	95.0	0.54	0.94
Week 1	98	-6.9	95	-10.4	97	-7.2	0.84	0.05
Week 2	97	-14.0	93	-15.7	95	-12.3	0.4	0.11
Week 3	88	-20.1	90	-23.4	93	-17.9	0.35	0.02
Week 4	87	-24.0	85	-26.4	91	-19.3	0.03	0.002
Week 5	86	-27.6	84	-30.4	88	-21.7	0.01	0.0003
Week 6	84	-30.6	84	-31.9	90	-22.3	0.0011	0.0002

*** The reported means are least square means. Source: Sponsor's Table CT-5.1.2.**

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/s/

Yeh-Fong Chen
7/26/2007 03:18:32 PM
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Peiling Yang
7/26/2007 03:20:47 PM
BIOMETRICS

Kooros Mahjoob
7/26/2007 03:57:09 PM
BIOMETRICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-436/S017

21-713/S012

21-729/S004

21-866/S004

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

DRUG: Abilify® Aripiprazole
PRIMARY REVIEWER: Andre Jackson
NDA: 21436/S-017
TYPE: NDA
FORMULATION: Tablet
STRENGTH: 10 20 and 30 mg
APPLICANT: BMS/Otsuka
Submission Dates: March 23, 2007, 2005

INDICATIONS: Schizophrenia (b) (4) in pediatric populations
Generic Name: Aripiprazole

INTRODUCTION

Abilify™ (aripiprazole, OPC-14597, BMS-337039) is approved in the United States of America (US) for the treatment in adults of acute schizophrenia (November 2002), maintenance of stability in schizophrenia (August 2003), treatment of acute manic and mixed episodes associated bipolar disorder (September 2004), and for the maintenance of efficacy in bipolar I disorder (March 2005).

The mechanism of action of aripiprazole differs from that of currently marketed typical and atypical antipsychotics. It has been **proposed that aripiprazole's efficacy in** schizophrenia is mediated through a combination of partial agonism/antagonism at dopamine D_2 and serotonin $5\text{-}HT_{1A}$ receptors, and antagonism at serotonin $5\text{-}HT_2$ receptors.

STUDY RATIONALE

In a previous study conducted in children and adolescents with conduct disorder, doses up to 15 mg QD were well tolerated. However, a maximum tolerated dose (MTD) in the pediatric population was not determined since it was not a defined objective of the protocol. The purpose of this study was to evaluate the safety and tolerability of doses greater than 15 mg and up to 30 mg in the pediatric population. Doses in excess of 30 mg were not studied due to limitations based upon the no-effect doses established in nonclinical toxicity studies in the most sensitive species.
Establishing an MTD in the pediatric population was desirable (b) (4)

OBJECTIVES

This study assessed the safety, tolerability, and PK of repeated doses of aripiprazole following oral administration to children and adolescent patients preferentially with a primary schizophrenia spectrum diagnosis or bipolar spectrum disorder.

TOLERABILITY

Dose toleration was defined as follows: during the course of the study the subject does

not experience any untoward events or potentially clinically significant changes from baseline in laboratory values, vital signs, ECG tracings, or EPS ratings, that are assessed as possibly related to the drug, and would warrant adjustment or discontinuation of the study drug. A dose level was judged to have been tolerated if 4 out of 6 (67%) of the subjects in a cohort with that maximum dose tolerated the dose.

METHODS

This study was conducted at the following centers:

Site 001

Robert Findling, MD
Director, Child and Adolescent Psychiatry
University Hospitals of Cleveland
Division of Child and Adolescent Psychiatry
11100 Euclid Avenue
Cleveland, OH 44106-5080

Site 002

Ralph Kauffman, MD
Marion Merrell Dow/Missouri Chair in Medical Research
Professor of Pediatrics and Pharmacology
Children's Mercy Hospital
2401 Gillham Road
Kansas City, MO 64108

Site 003

Floyd R. Sallee, MD, PhD
Director, Division of Child Psychiatry
Professor of Psychiatry and Pediatrics
University of Cincinnati College of Medicine
425 Oak Street
Sallee Study Group / Carriage House
Cincinnati, OH 45219

Table1.-Demographic Characteristics

Parameter	Statistic	ARIP 20 mg (N = 8)	ARIP 25 mg (N = 7)	ARIP 30 mg (N = 6)	Total (N = 21)
Age (years)	Mean (SD)	12.4 (2.5)	13.3 (1.8)	10.8 (1.2)	12.2 (2.1)
	Range	10 - 17	11 - 16	10 - 13	10 - 17
Weight (kg)	Mean (SD)	59.50 (18.99)	71.43 (20.68)	50.22 (21.71)	60.82 (21.13)
	Range	36.4 - 83.0	45.1 - 100.0	31.3 - 89.9	31.3 - 100.0
Height (cm)	Mean (SD)	154.0 (9.5)	166.1 (9.2)	147 (12.0)	156.1 (12.4)
	Range	142 - 173	157 -180	134 - 167	134 - 180
BMI	Mean (SD)	24.8 (7.1)	25.8 (7.0)	22.8 (7.2)	24.6 (6.8)
	Range	16.2 - 34.8	16.8 - 33.1	15.5 - 32.2	15.5 - 34.8
Gender	n (%)				
Male		4 (50%)	4 (57%)	6 (100%)	14 (67%)
Female		4 (50%)	3 (43%)	0 (0%)	7 (33%)
Race	n (%)				
Caucasian		6 (75%)	4 (57%)	6 (100%)	16 (76%)
Black or African American		1 (13%)	3 (43%)	0 (0%)	4 (19%)
Other		1 (13%)	0 (0%)	0 (0%)	1 (5%)
Ethnicity	n (%)				
Hispanic/Latino		0 (0%)	2 (29%)	0 (0%)	2 (10%)
Not Hispanic/Latino		8 (100%)	5 (71%)	6 (100%)	19 (90%)

Overall Design and Plan of the Study

This was a multicenter, open-label, sequential cohort, dose-escalation study of multiple doses of aripiprazole ranging from 2 mg to 30 mg. Up to 24 subjects could have participated. Children and adolescent subjects preferentially with a primary schizophrenia diagnosis or bipolar spectrum disorder were eligible to participate in this study. Three cohorts of 6 subjects each were to be administered aripiprazole for up to 12 days (depending upon the maximum dose for the cohort) using a forced titration scheme to achieve one of the following dose levels: 20 mg, 25 mg, and 30 mg. Following the dose-escalation phase, subjects entered the fixed-dose phase and received the maximum dose for that cohort for 14 days.

The dosing schedule for each cohort is outlined in Table 2

Table 2. Dosing Schedule for Dose-escalation and fixed-dose phases.

Cohort	Dose-escalation Phase	Fixed-dose Phase
20 mg Cohort (n = 6)	2 mg × 2 days, 5 mg × 2 days, 10 mg × 2 days, 15 mg × 2 days	20 mg × 14 days
25 mg Cohort (n = 6)	2 mg × 2 days, 5 mg × 2 days, 10 mg × 2 days, 15 mg × 2 days, 20 mg × 2 days	25 mg × 14 days
30 mg Cohort (n = 6)	2 mg × 2 days, 5 mg × 2 days, 10 mg × 2 days, 15 mg × 2 days, 20 mg × 2 days, 25 mg × 2 days	30 mg × 14 days

Pharmacokinetic/Pharmacodynamic Assessments

Blood was collected for the determination of aripiprazole plasma concentrations. Samples (4 mL) were taken on Days 14 and 15 of the fixed-dose phase at predose and at the following postdose hours: 1, 2, 3, 4, 6, 8, 10, and 24 hours. Specific information regarding sample handling and processing is provided in an appendix to the study protocol

Pharmacokinetics

For each subject, the aripiprazole and dehydro-aripiprazole plasma concentration-time data were analyzed using a noncompartmental method. Actual blood sample times were used for PK calculations. Missing time zero values were imputed using the 24-hour postdose value as the dosing interval was 24 hours. Values for $C_{ss,max}$ and t_{max} were taken directly from the observed data. Values of AUC_τ were estimated using the linear trapezoidal rule to the actual time of the 24-hour sample. Values of CL_{ss}/F for aripiprazole were determined using standard methods

(b) (4)

(b) (4)

Results

Table 3. Tolerability Results During the Dose-Escalation Phase, as Assessed by Majority Vote of Principal Investigators

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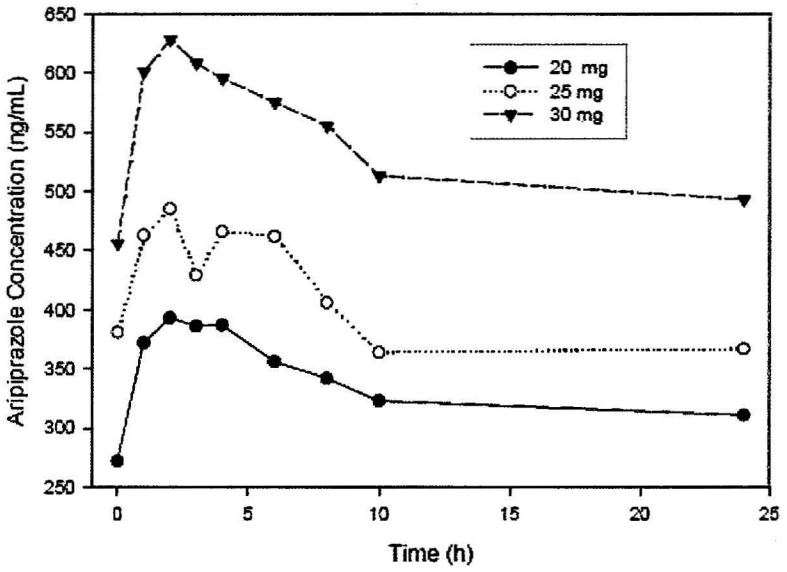

Figure 1. Mean Aripiprazole Plasma Concentrations Following Multiple Oral QD Dosing of Aripiprazole in Children and Adolescent Subjects

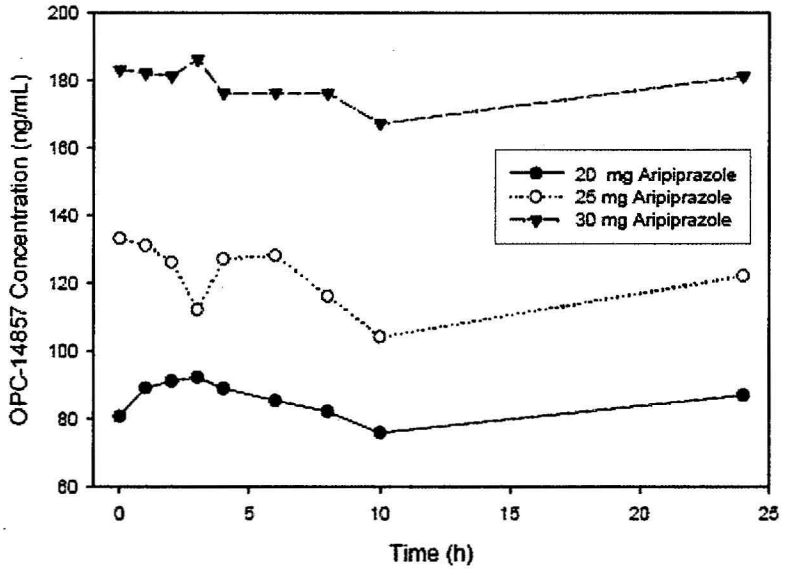

Figure 2. Mean Dehydro-aripiprazole Plasma Concentrations Following Multiple Oral QD Dosing of Aripiprazole in Children and Adolescent Subjects

Table 4. Mean (SD) Plasma Pharmacokinetic Parameters for Aripiprazole Following Multiple Oral QD Dosing of Aripiprazole in Children and Adolescent Subjects

Parameter	ARIP 20 mg (N = 6)	ARIP 25 mg (N = 5)	ARIP 30 mg (N = 6)
$C_{ss,max}$ (ng/mL)	435 (137)	529 (341)	653 (213)
t_{max} (h)[a]	2.00 (1.00-24.08)	2.05 (1.00-4.02)	2.00 (1.00- 8.00)
AUC_τ (ng·h/mL)	8031 (3745)	9488 (7001)	12770 (5444)
CL_{ss}/F (mL/h/kg)	51.7 (22.0)	50.4 (25.9)	58.8 (27.7)

[a]Values are median (minimum - maximum).

Table 5. Mean (SD) Plasma Pharmacokinetic Parameters for Dehydro-aripiprazole Following Multiple Oral QD Dosing of Aripiprazole in Children and Adolescent Subjects

Parameter	ARIP 20 mg (N = 6)	ARIP 25 mg (N = 5)	ARIP 30 mg (N = 6)
$C_{ss,max}$ (ng/mL)	99.7 (38.3)	141 (51.0)	202 (63.6)
t_{max} (h)[a]	2.51 (1.00-24.08)	4.02 (1.00-24.03)	2.00 (0- 8.00)
AUC_τ (ng·h/mL)	1995 (711)	2801 (1190)	4208 (1287)
AUC_τ[b] ratio	0.248	0.295	0.330

[a]Values are median (minimum - maximum).

[b]Ratio of mean dehydro-aripiprazole AUC_τ to aripiprazole AUC_τ

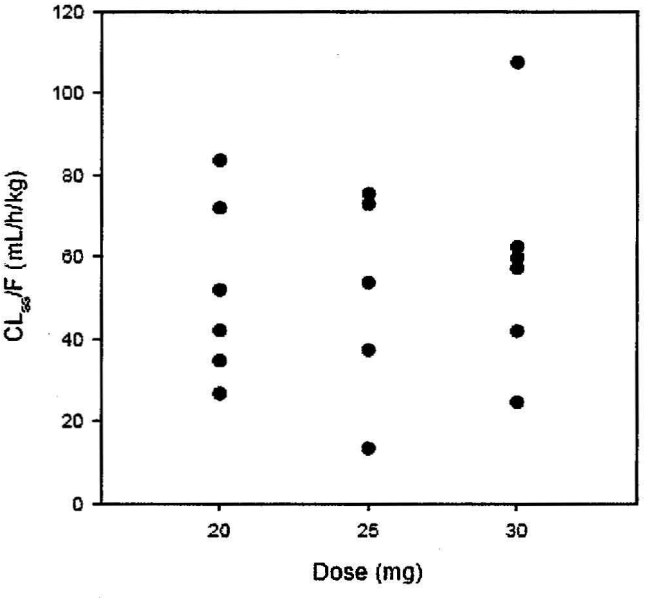

Figure 3 Values of CLss/F Versus Dose Following Multiple Oral QD Dosing of Aripiprazole in Children and Adolescent Subjects

CONCLUSIONS

1.There appears to be trend of decreased clearance with dose but it is difficult to verify with 24 subjects although the firm states that the drug appears to be linear. AUC and Cmax appear to be linear although the firm did not do a log analysis of the dose data so linearity appears likely but not definitively determined.

___2____ Page (s) Withheld

____ Trade Secret / Confidential (b4)

_✓_ Draft Labeling (b4)

____ Draft Labeling (b5)

____ Deliberative Process (b5)

(b) (4)

FDA LABEL-Comments

The firm's proposed label only contained changes to the label by adding pediatric information which is supported by recent pediatric studies. The other portions of the label related to Drug-drug interactions and Clinical Pharmacology are identical to the currently approved label

Andre Jackson_____
Reviewer, Psychopharmacological Drug Section, DCP I
Office of Clinical Pharmacology and Biopharmaceutics

RD/FTinitialized by Raman Baweja, Ph.D._____

Team Leader, Psychiatry Drug Section, DCP I
Office of Clinical Pharmacology
cc: NDA 21-436/S017, HFD-860(Mehta, Baweja, Jackson)

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/s/

Andre Jackson
8/22/2007 02:10:24 PM
BIOPHARMACEUTICS

Raman Baweja
8/22/2007 02:55:39 PM
BIOPHARMACEUTICS

Clinical Pharmacology/Biopharmaceutics Review

PRODUCT (Generic Name):	Aripiprazole
PRODUCT (Brand Name):	Abilify
DOSAGE FORM:	Tablets
DOSAGE STRENGTHS:	**2MG; 5MG 10MG; 15MG; 20MG; 30MG;**
NDA:	21436/S017
NDA TYPE:	Labelling
SUBMISSION DATE:	March 23, 2007
SPONSOR:	Otsuka
REVIEWER	Andre Jackson

REVIEW OF LABELLING

OVERALL LABEL COMMENT:

THE LABEL PRESENTED IN THIS REVIEW IS THE FIRM'S PROPOSED PLR FORMAT WITH REVIEWER COMMENTS, INSERTIONS, AND DELETIONS. INCLUSION OF THE INSERTIONS AND DELETIONS WOULD MAKE THIS LABEL ACCEPTABLE TO OCP

(b) (4)

___10____ Page (s) Withheld

____ Trade Secret / Confidential (b4)

_✓_ Draft Labeling (b4)

____ Draft Labeling (b5)

____ Deliberative Process (b5)

(b) (4)

SIGNATURES

Andre Jackson_____

Reviewer, Psychopharmacological Drug Section, DCP I
Office of Clinical Pharmacology and Biopharmaceutics

RD/FTinitialized by Raman Baweja, Ph.D._____

Team Leader, Psychiatry Drug Section, DCP I
Office of Clinical Pharmacology
cc: NDA 21-436/S017, HFD-860(Mehta, Baweja, Jackson)
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/s/

Andre Jackson
9/10/2007 10:44:08 AM
BIOPHARMACEUTICS

Raman Baweja
9/10/2007 11:59:58 AM
BIOPHARMACEUTICS

Clinical Pharmacology/Biopharmaceutics Review
BPCA Summary Review

PRODUCT (Generic Name):	Aripiprazole
PRODUCT (Brand Name):	Abilify
DOSAGE FORM:	Tablets
DOSAGE STRENGTHS:	10mg, 20mg, 30 mg,
NDA:	21436/S-017
NDA TYPE:	Supplement for **Schizophrenia** in children and adolescents in response to FDA Pediatric Written Request Letter
SUBMISSION DATE:	March 23, 2007
SPONSOR:	Otsuka
OND DIVISION:	Psychiatry

EXECUTIVE SUMMARY

Aripiprazole is currently indicated in the treatment of acute schizophrenia in adults. In a previous study conducted in children and adolescents with conduct disorder, doses up to 15 mg QD were well tolerated. However, the safety and tolerability of doses higher than 15 mg had not been determined in children and adolescents. Results from the current dose escalation multiple dose study indicates that doses up to 30 mg/day are safe and tolerated in children and adolescents .

This sNDA includes a dose escalation multiple dose study to final targeted doses of 20 mg, 25 mg and 30 mg of aripiprazole.

The overall conclusion from the pharmacokinetic studies in adolescents and children was:

- The pharmacokinetics are linear in children and adolescents from 20mg to 30 mg.

RECOMMENDATION

From a Clinical Pharmacology/Biopharmaceutics perspective this sNDA is acceptable with the labeling changes suggested by the reviewer.

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/s/

Andre Jackson
9/10/2007 12:48:23 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-436/S017

21-713/S012

21-729/S004

21-866/S004

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 21-436 (S-017); 21-713 (S-012); 21-729 (S-004); 21-866 (S-004) SUPPL#

See NDA # HFD # 130

Trade Name Abilify

Generic Name aripiprazole tablets, orally disintegrating tablets, oral solution, im injection

Applicant Name Otsuka Pharmaceutical Company, Ltd.

Approval Date, If Known 10/29/2007

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

SE5

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

YES ☒ NO ☐

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

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

d) Did the applicant request exclusivity?

YES ☐ NO ☒

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

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

YES ☐ NO ☒

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

No, but it is the first portion submitted to fullfill the WR, S-021 oof NDA 21436 is the 2nd.

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

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

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES ☒ NO ☐

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

NDA# NDA 21-436
NDA 21-713
NDA 21-729
NDA 21-866
NDA#

NDA#

2. Combination product.

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

YES ☐ NO ☒

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

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical

investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☒ NO ☐

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

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

YES ☒ NO ☐

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

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

YES ☐ NO ☒

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

YES ☐ NO ☒

If yes, explain:

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

YES ☐ NO ☒

If yes, explain:

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

Study 31-03-239 and Study 31-03-241

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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

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

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☒

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

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

Investigation #1	YES ☐	NO ☒
Investigation #2	YES ☐	NO ☒

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

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

Study 31-03-239 and Study 31-03-241

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

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

Investigation #1 !

IND # 42776 YES ☒ ! NO ☐

! Explain:

Investigation #2 !

IND # 42776 YES ☒ ! NO ☐

! Explain:

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

Investigation #1 !

YES ☐ Explain:	! NO ☐ ! Explain:
Investigation #2 YES ☐ Explain:	! ! ! NO ☐ ! Explain:

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

YES ☐ NO ☒

If yes, explain:

==========

Name of person completing form: Keith Kiedrow, PharmD
Title: Regulatory Project Manager
Date: 2-15-08

Name of Office/Division Director signing form: Thomas Laughren, MD
Title: Director, Division of Psychiatry Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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/s/

Thomas Laughren
2/15/2008 05:00:20 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : NDA 21-436 S-017; NDA 21-713 S-012; NDA 21-729 S-004; NDA 21-866 S-004
Supplement Type (e.g. SE5): SE5

Stamp Date: 10/29/2007 **PDUFA Goal Date: 12/1/2007**

HFD 130 **Trade and generic names/dosage form: Abilify (aripiprazole) Tablets, Orally Disintegrating Tablets, Oral Solution, and Injection**

Applicant: Otsuka **Therapeutic Class:** 2020200

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

- X Yes. Please proceed to the next question.
- ☐ No. PREA does not apply. Skip to signature block.

** SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.*

Indication(s) *previously approved* (please complete this section for supplements only): Schizophrenia in adults; bipolar disorder in adults, adjunctive treatment of major depressive disorder in adults

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): 3

Indication #1: treatment of schizophrenia

Is this an orphan indication?

- ☐ Yes. PREA does not apply. Skip to signature block.
- X No. Please proceed to the next question.

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

- ☐ Yes: Please proceed to Section A.

X No: Please check all that apply: ___Partial Waiver ___Deferred X Completed

NOTE: More than one may apply

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

Section A: Fully Waived Studies

Reason(s) for full waiver:

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

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

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min_____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____
Reason(s) for partial waiver:

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

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

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

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

Other:_____

Date studies are due (mm/dd/yy): _____

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

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Ages 13 – 17 years.

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

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

This page was completed by: Keith Kiedrow

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: (b) (4)

Is this an orphan indication?

Yes. PREA does not apply. Skip to signature block.

X **No. Please proceed to the next question.**

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

☐ **Yes: Please proceed to Section A.**

X **No: Please check all that apply: ___Partial Waiver _X_Deferred (ongoing at the time of this approval) ___Completed**

NOTE: More than one may apply

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

Section A: Fully Waived Studies

Reason(s) for full waiver:

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

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

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below)::

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for partial waiver:

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

- ❑ **Formulation needed**
- ❑ **Other:**_____

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

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):: 10-17 years

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for deferral:

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

Date studies are due (mm/dd/yy): _____

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

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Comments:

Indication #3: _ Adjunctive treatment of (b) (4)

Is this an orphan indication?

Yes. PREA does not apply. Skip to signature block.

X **No. Please proceed to the next question.**

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

X Yes: Please proceed to Section A.

No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

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

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

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below)::

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for partial waiver:

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

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

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below)::

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

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

Date studies are due (mm/dd/yy): _____

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

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

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/s/

Keith Kiedrow
4/14/2009 05:30:56 PM