ABILIFY® Tablets
ABILIFY® Oral Solution
ABILIFY DISCMELT® Orally Disintegrating Tablets
(Aripiprazole)

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

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. ABILIFY (aripiprazole) is not approved for the treatment of patients with dementia-related psychosis *[see Warnings and Precautions (5.1)]*.

Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term studies. These studies did not show an increase in the risk of suicidal thoughts and behaviour with antidepressants use in patients over age 24; there was a reduction in risk with antidepressants use in patients aged 65 and older. [see *Warnings and Precautions (5.3)*].

In patients of all ages who are started on antidepressant therapy, monitor closely for worsening, and for emergence of suicidal thoughts and behavior. Advise families and caregivers of the need for close observation and communication with the prescriber. *[see Warnings and Precautions (5.3)]*.

1 INDICATIONS AND USAGE

1.1 Schizophrenia

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

1.2 Bipolar I Disorder

Acute Treatment of Manic and Mixed Episodes

ABILIFY is indicated for the acute treatment of manic and mixed episodes associated with bipolar I disorder, both as monotherapy and as an adjunct to lithium or valproate.

Efficacy as monotherapy was established in four 3-week monotherapy trials in adults and one 4-week monotherapy trial in pediatric patients (10 to 17 years). Efficacy as adjunctive therapy was established in one 6-week adjunctive trial in adults [*see Clinical Studies (14.2)]*.

Maintenance Treatment of Bipolar I Disorder

ABILIFY is indicated for the maintenance treatment of bipolar I disorder, both as monotherapy and as an adjunct to either lithium or valproate. Maintenance efficacy was demonstrated in one monotherapy maintenance trial and in one adjunctive maintenance trials in adults. [*see Clinical Studies (14.2)]*.

1.3 Adjunctive Treatment of Major Depressive Disorder

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

1.4 Irritability Associated with Autistic Disorder

ABILIFY is indicated for the treatment of irritability associated with autistic disorder. Efficacy was established in two 8-week trials in pediatric patients (aged 6 to 17 years) with irritability associated with autistic disorder (including symptoms of aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods) *[see Clinical Studies (14.4)]*.

1.5 Tourette's Disorder

ABILIFY is indicated for the treatment of Tourette's disorder. Efficacy was established in one 10-week placebo-controlled trials in pediatric patients (6 to 18 years) with Tourette's disorder.

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

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

2 DOSAGE AND ADMINISTRATION

2.1 Schizophrenia

Adults

The recommended starting and target dose for ABILIFY is 10 or 15 mg/day administered on a once-a-day schedule without regard to meals. ABILIFY has been systematically evaluated and shown to be effective in a dose range of 10 to 30 mg/day, when administered as the tablet formulation; however, doses higher than 10 or 15 mg/day were not more effective than 10 or 15 mg/day. Dosage increases should generally not be made before 2 weeks, the time needed to achieve steady-state *[see Clinical Studies (14.1)]*.

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

Adolescents

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

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

Switching from Other Antipsychotics

There are no systematically collected data to specifically address switching patients with schizophrenia from other antipsychotics to ABILIFY or concerning concomitant

administration with other antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some patients with schizophrenia, more gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized.

2.2 Bipolar I Disorder

Acute treatment of Manic and Mixed Episodes

Adults: The recommended starting dose in adults is 15 mg given once daily as monotherapy and 10 to 15 mg given once daily as adjunctive therapy with lithium or valproate. ABILIFY can be given without regard to meals. The recommended target dose of ABILIFY is 15 mg/day as monotherapy or as adjunctive therapy with lithium or valproate. The dose may be increased to 30 mg/day based on clinical response. The safety of doses above 30 mg/day has not been evaluated in clinical trials.

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

Maintenance Treatment

The recommended dose for maintenance treatment, whether as monotherapy or as adjunctive therapy, is the same dose needed to stabilized patients during acute treatment, both for adults and pediatric patients. Patients should be periodically reassessed to determine the continued need for maintenance treatment.

2.3 Adjunctive Treatment of Major Depressive Disorder

Adults

The recommended starting dose for ABILIFY as adjunctive treatment for patients already taking an antidepressant is 2 to 5 mg/day. The recommended dosage range is 2 to 15 mg/day. Dosage adjustments of up to 5 mg/day should occur gradually, at intervals of no less than 1 week *[see Clinical Studies (14.3)]*.

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

2.4 Irritability Associated with Autistic Disorder

Pediatric Patients (6 to 17 years)

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

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

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

2.5 Tourette's Disorder

Pediatric Patients (6 to 18 years)

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

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

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

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

2.6 Dosage Adjustments for Cytochrome P450 Considerations

Dosage adjustments are recommended in patients who are known CYP2D6 poor metabolizers and in patients taking concomitant CYP3A4 inhibitors or CYP2D6 inhibitors or strong CYP3A4 inducers (see Table 1). When the CYP3A4 and/or CYP2D6 inhibitor is withdrawn from the combination therapy, ABILIFY dosage should be increased. When the CYP3A4 inducer is withdrawn from the combination therapy, ABILIFY dosage should be reduced to 10 mg to 15 mg. Patients who may be receiving a

combination of strong, moderate, and a weak inhibitors of CYP3A4 and CYP2D6 (e.g., a strong CYP3A4 inhibitor and a moderate CYP2D6 inhibitor or a moderate CYP3A4 inhibitor with a moderate CYP2D6 inhibitor), the dosing maybe reduced to one-quarter (25%) of the usual dose initially and then adjusted to achieve a favorable clinical response.

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

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

When adjunctive ABILIFY is administered to patients with major depressive disorder, ABILIFY should be administered without dosage adjustment as specified in *Dosage and Administration* (2.3)

2.7 Dosing of Oral Solution

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

2.8 Dosing of Orally Disintegrating Tablets

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

3 DOSAGE FORMS AND STRENGTHS

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

Table 2: ABILIFY Tablet Presentations

Tablet Strength	Tablet Color/Shape	Tablet Markings
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"

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.

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1. Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Increased Mortality

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

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

In three, 10-week, placebo-controlled studies of ABILIFY in elderly patients with psychosis associated with Alzheimer's disease (n=938; mean age: 82.4 years; range: 56-99 years), the 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%, ABILIFY 5%], somnolence (including sedation) [placebo 3%, ABILIFY 8%], and incontinence (primarily, urinary incontinence) [placebo 1%, ABILIFY 5%], excessive salivation [placebo 0%, ABILIFY 4%], and lightheadedness [placebo 1%, ABILIFY 4%].

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

5.2 Cerebrovascular Adverse Events, Including Stroke

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

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

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

suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

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

Table 4:

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

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

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

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

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for MDD as well as for other indications, both psychiatric and nonpsychiatric. Although a

causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

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

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

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

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

5.4 Neuroleptic Malignant Syndrome (NMS)

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

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both

serious medical illness (e.g., pneumonia, systemic infection) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

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

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

5.5 Tardive Dyskinesia

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

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

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

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

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

5.6 Metabolic Changes

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

Hyperglycemia/Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. There have been 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 reactions 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 reactions in patients treated with atypical antipsychotics are not available.

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

Adults

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

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

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

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

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

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

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

Pediatric Patients and Adolescents

In an analysis of two placebo-controlled trials in adolescents with schizophrenia (13 to 17 years) and pediatric patients with bipolar disorder (10 to 17 years), the mean change in

fasting glucose in ABILIFY-treated patients (+4.8 mg/dL; with a median exposure of 43 days; N=259) was not significantly different than in placebo-treated patients (+1.7 mg/dL; with a median exposure of 42 days; N=123).

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

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

Dyslipidemia

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

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

Adults

Table 7 shows the proportion of adult patients, primarily from pooled schizophrenia and bipolar disorder monotherapy placebo-controlled trials, with changes in total cholesterol (pooled from 17 trials; median exposure 21 to 25 days), fasting triglycerides (pooled from eight trials; median exposure 42 days), fasting LDL cholesterol (pooled from eight trials; median exposure 39 to 45 days, except for placebo-treated patients with baseline normal fasting LDL measurements, who had median treatment exposure of 24 days) and HDL cholesterol (pooled from nine trials; median exposure 40 to 42 days).

Table 7: Changes in Blood Lipid Parameters From Placebo-Controlled Monotherapy Trials in Adults

	Treatment Arm	n/N	%
Total Cholesterol	ABILIFY	34/1357	2.5
Normal to High	Placebo	27/973	2.8
(<200 mg/dL to ≥240 mg/dL)			

Fasting Triglycerides Normal to High (<150 mg/dL to ≥200 mg/dL)	ABILIFY Placebo	40/539 30/431	7.4 7.0
Fasting LDL Cholesterol Normal to High (<100 mg/dL to ≥160 mg/dL)	ABILIFY Placebo	2/332 2/268	0.6 0.7
HDL Cholesterol Normal to Low (≥40 mg/dL to <40 mg/dL)	ABILIFY Placebo	121/1066 77/794	11.4 12.5

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

Table 8 shows the proportion of patients with changes in total cholesterol (fasting/nonfasting), fasting triglycerides, fasting LDL cholesterol, and HDL cholesterol from two placebo-controlled adjunctive trials in adult patients with major depressive disorder (median exposure 42 days).

Table 8: Changes in Blood Lipid Parameters From Placebo-Controlled Adjunctive Trials in Adult Patients with Major Depressive Disorder

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

Pediatric Patients and Adolescents

Table 9 shows the proportion of adolescents with schizophrenia (13 to 17 years) and pediatric patients with bipolar disorder (10 to 17 years) with changes in total cholesterol and HDL cholesterol (pooled from two placebo-controlled trials; median exposure 42 to 43 days) and fasting triglycerides (pooled from two placebo-controlled trials; median exposure 42 to 44 days).

Table 9: Changes in Blood Lipid Parameters From Placebo-Controlled Monotherapy Trials in Pediatric and Adolescent Patients in Schizophrenia and Bipolar Disorder

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

In monotherapy trials of adolescents with schizophrenia and pediatric patients with bipolar disorder, the proportion of patients at 12 weeks and 24 weeks with changes from Normal to High in total cholesterol (fasting/nonfasting), fasting triglycerides, and fasting LDL cholesterol were similar between ABILIFY- and placebo-treated patients: at 12 weeks, Total Cholesterol (fasting/nonfasting), 0/57 (0%) vs. 0/15 (0%); Fasting Triglycerides, 2/72 (2.8%) vs. 1/14 (7.1%), respectively; and at 24 weeks, Total Cholesterol (fasting/nonfasting), 0/36 (0%) vs. 0/12 (0%); Fasting Triglycerides, 1/47 (2.1%) vs. 1/10 (10.0%), respectively.

Table 10 shows the proportion of patients with changes in total cholesterol (fasting/nonfasting) and fasting triglycerides (median exposure 56 days) and HDL cholesterol (median exposure 55 to 56 days) from two placebo-controlled trials in pediatric patients (6 to 17 years) with irritability associated with autistic disorder.

Table 10: Changes in Blood Lipid Parameters From Placebo-Controlled Trials in Pediatric Patients with Autistic Disorder

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

Weight Gain

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

Adults

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

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

Pediatric Patients and Adolescents

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

5.7 Pathological Gambling and Other Compulsive Behaviors

Post-marketing case reports suggest that patients can experience intense urges, particularly for gambling, and the inability to control these urges while taking aripiprazole. Other compulsive urges, reported less frequently, include: sexual urges, shopping, eating or binge eating, and other impulsive or compulsive behaviors. Because patients may not recognize these behaviors as abnormal, it is important for prescribers to ask patients or their caregivers specifically about the development of new or intense gambling urges, compulsive sexual urges, compulsive shopping, binge or compulsive eating, or other urges while being treated with aripiprazole. It should be noted that impulse-control symptoms can be associated with the underlying disorder. In some cases, although not all, urges were reported to have stopped when the dose was reduced or the medication was discontinued. Compulsive behaviors may result in harm to the patient and others if not recognized. Consider dose reduction or stopping the medication if a patient develops such urges.

5.8 Orthostatic Hypotension

ABILIFY may cause orthostatic hypotension, perhaps due to its α_1-adrenergic receptor antagonism. The incidence of orthostatic hypotension-associated events from short-term, placebo-controlled trials of adult patients on oral ABILIFY (n=2467) included (ABILIFY incidence, placebo incidence) orthostatic hypotension (1%, 0.3%), postural dizziness (0.5%, 0.3%), and syncope (0.5%, 0.4%); of pediatric patients 6 to 17 years of age (n=611) on oral ABILIFY included orthostatic hypotension (0.5%, 0%), postural dizziness (0.3%, 0%), and syncope (0.2%, 0%). *[see Adverse Reactions (6.1)]*.

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

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

5.9 Falls

Antipsychotics, including ABILIFY, may cause somnolence, postural hypotension, motor and sensory instability, which may lead to falls and, consequently, fractures or other injuries. For patients with diseases, conditions, or medications that could exacerbate these effects, complete fall risk assessments when initiating antipsychotic treatment and recurrently for patients on long-term antipsychotic therapy.

5.10 Leukopenia, Neutropenia, and Agranulocytosis

In clinical trial and/or post-marketing experience, events of leukopenia/neutropenia have been reported temporally related to antipsychotic agents, including ABILIFY. Agranulocytosis has also been reported.

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) and history of drug-induced leukopenia/neutropenia. Patients with a history of a clinically significant low WBC or drug-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of ABILIFY should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Monitor patients with clinically significant neutropenia for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Discontinue ABILIFY in patients with severe neutropenia (absolute neutrophil count <1000/mm^3) and follow their WBC counts until recovery.

5.11 Seizures/Convulsions

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

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

5.12 Potential for Cognitive and Motor Impairment

ABILIFY, like other antipsychotics, may have the potential to impair judgment, thinking, or motor skills. For example, in short-term, placebo-controlled trials, somnolence (including sedation) was reported as follows (aripiprazole incidence, placebo incidence):

in adult patients (n=2467) treated with oral ABILIFY (11%, 6%), and in pediatric patients ages 6 to 17 (n=611) (24%, 6%). Somnolence (including sedation) led to discontinuation in 0.3% (8/2467) of adult patients and 3% (15/611) of pediatric patients (6 to 17 years) on oral ABILIFY in short-term, placebo-controlled trials.

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.

5.13 Body Temperature Regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing ABILIFY for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, (e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration) *[see Adverse Reactions (6.2)]*.

5.14 Suicide

The possibility of a suicide attempt is inherent in psychotic illnesses, bipolar disorder, and major depressive disorder, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for ABILIFY should be written for the smallest quantity consistent with good patient management in order to reduce the risk of overdose *[see Adverse Reactions (6.1, 6.2)]*.

5.15 Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use, including ABILIFY. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. ABILIFY and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia *[see Warnings and Precautions (5.1) and Adverse Reactions (6.2)]*.

5.16 Use in Patients with Concomitant Illness

Clinical experience with ABILIFY in patients with certain concomitant systemic illnesses is limited *[see Use in Specific Population (8.6)]*.

ABILIFY has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies *[see Warnings and Precautions (5.1, 5.6)]*.

6 ADVERSE REACTIONS

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

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

- Increased Mortality in Elderly Patients with Dementia-Related Psychosis *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Cerebrovascular Adverse Events, Including Stroke *[see Warnings and Precautions (5.2)]*
- Suicidal Thoughts and Behaviors in Children, Adolescents, and Young Adults *[see Boxed Warning and Warnings and Precautions (5.3)]*
- Neuroleptic Malignant Syndrome (NMS) *[see Warning and Precautions (5.4)]*
- Tardive Dyskinesia *[see Warning and Precautions (5.5)]*
- Metabolic Changes *[see Warnings and Precautions (5.6)]*
- Pathological Gambling and Other Compulsive Behaviors *[see Warning and Precautions (5.7)]*
- Orthostatic Hypotension *[see Warning and Precautions (5.8)]*
- Falls *[see Warning and Precautions (5.9)]*
- Leukopenia, Neutropenia, and Agranulocytosis *[see Warning and Precautions (5.10)]*
- Seizures/Convulsions *[see Warning and Precautions (5.11)]*
- Potential for Cognitive and Motor Impairment *[see Warning and Precautions (5.12)]*
- Body Temperature Regulation *[see Warning and Precautions (5.13)]*
- Suicide *[see Warning and Precautions (5.14)]*
- Dysphagia *[see Warning and Precautions (5.15)]*
- Use in Patients with Concomitant Illness *[see Warning and Precautions (5.16)]*

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

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

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

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

The conditions and duration of treatment with ABILIFY (monotherapy and adjunctive therapy with antidepressants or mood stabilizers) included (in overlapping categories) double-blind, comparative and noncomparative open-label studies, inpatient and outpatient studies, fixed- and flexible-dose studies, and short- and longer-term exposure.

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.

6.1 Clinical Trials Experience

Adult patients with Schizophrenia

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

Adverse Reactions Associated with Discontinuation of Treatment

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

Commonly Observed Adverse Reactions

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

Adult Patients with Bipolar Mania

Monotherapy

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

Adverse Reactions Associated with Discontinuation of Treatment

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

Commonly Observed Adverse Reactions

Commonly observed adverse reactions associated with the use of ABILIFY in patients with bipolar mania (incidence of 5% or greater and aripiprazole incidence at least twice that for placebo) are shown in Table 11.

Table 11: Commonly Observed Adverse Reactions in Short-Term, Placebo-Controlled Trials of Adult Patients with Bipolar Mania Treated with Oral ABILIFY Monotherapy

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

Less Common Adverse Reactions in Adults

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

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

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

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

Adult Patients with Adjunctive Therapy with Bipolar Mania

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

Adverse Reactions Associated with Discontinuation of Treatment

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

Commonly Observed Adverse Reactions

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

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

Table 13 enumerates the incidence, rounded to the nearest percent, of adverse reactions that occurred during acute treatment (up to 6 weeks), including only those reactions that occurred in 2% or more of patients treated with adjunctive ABILIFY (doses of 15 or 30 mg/day) and lithium or valproate and for which the incidence in patients treated with this combination was greater than the incidence in patients treated with placebo plus lithium or valproate.

Table 13: Adverse Reactions in a Short-Term, Placebo-Controlled Trial of Adjunctive Therapy in Patients with Bipolar Disorder

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

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

Pediatric Patients (13 to 17 years) with Schizophrenia

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

Adverse Reactions Associated with Discontinuation of Treatment

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

Commonly Observed Adverse Reactions

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

Pediatric Patients (10 to 17 years) with Bipolar Mania

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

Adverse Reactions Associated with Discontinuation of Treatment

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

Commonly Observed Adverse Reactions

Commonly observed adverse reactions associated with the use of ABILIFY in pediatric patients with bipolar mania (incidence of 5% or greater and ABILIFY incidence at least twice that for placebo) are shown in Table 14.

Table 14: Commonly Observed Adverse Reactions in Short-Term, Placebo-Controlled Trials of Pediatric Patients (10 to 17 years) with Bipolar Mania Treated with Oral ABILIFY

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

Pediatric Patients (6 to 17 years) with Autistic Disorder

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

Adverse Reactions Associated with Discontinuation of Treatment

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

Commonly Observed Adverse Reactions

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

Table 15: Commonly Observed Adverse Reactions in Short-Term, Placebo-Controlled Trials of Pediatric Patients (6 to 17 years) with Autistic Disorder Treated with Oral ABILIFY

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

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

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

Adverse Reactions Associated with Discontinuation of Treatment

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

Commonly Observed Adverse Reactions

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

Table 16: Commonly Observed Adverse Reactions in Short-Term, Placebo-Controlled Trials of Pediatric Patients (6 to 18 years) with Tourette's Disorder Treated with Oral ABILIFY

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

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

Table 17 enumerates the pooled incidence, rounded to the nearest percent, of adverse reactions that occurred during acute therapy (up to 6 weeks in schizophrenia, up to 4 weeks in bipolar mania, up to 8 weeks in autistic disorder, and up to 10 weeks in Tourette's disorder), including only those reactions that occurred in 2% or more of pediatric patients treated with ABILIFY (doses ≥2 mg/day) and for which the incidence in patients treated with ABILIFY was greater than the incidence in patients treated with placebo.

Table 17: Adverse Reactions in Short-Term, Placebo-Controlled Trials of Pediatric Patients (6 to 18 years) Treated with Oral ABILIFY

	Percentage of Patients Reporting Reaction[a]	
System Organ Class	**Aripiprazole**	**Placebo**
Preferred Term	**(n=732)**	**(n=370)**
Eye Disorders		
Blurred Vision	3	0
Gastrointestinal Disorders		
Abdominal Discomfort	2	1
Vomiting	8	7
Nausea	8	4
Diarrhea	4	3
Salivary Hypersecretion	4	1
Abdominal Pain Upper	3	2
Constipation	2	2
General Disorders and Administration Site Conditions		
Fatigue	10	2
Pyrexia	4	1

System Organ Class Preferred Term	Aripiprazole (n=732)	Placebo (n=370)
Irritability	2	1
Asthenia	2	1
Infections and Infestations		
Nasopharyngitis	6	3
Investigations		
Weight Increased	3	1
Metabolism and Nutrition Disorders		
Increased Appetite	7	3
Decreased Appetite	5	4
Musculoskeletal and Connective Tissue Disorders		
Musculoskeletal Stiffness	2	1
Muscle Rigidity	2	1
Nervous System Disorders		
Somnolence	16	4
Headache	12	10
Sedation	9	2
Tremor	9	1
Extrapyramidal Disorder	6	1
Akathisia	6	4
Drooling	3	0
Lethargy	3	0
Dizziness	3	2
Dystonia	2	1
Respiratory, Thoracic, and Mediastinal Disorders		
Epistaxis	2	1
Skin and Subcutaneous Tissue Disorders		
Rash	2	1

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

Adult Patients Receiving ABILIFY as Adjunctive Treatment of Major Depressive Disorder

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

Adverse Reactions Associated with Discontinuation of Treatment

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

Commonly Observed Adverse Reactions

The commonly observed adverse reactions associated with the use of adjunctive ABILIFY in patients with major depressive disorder (incidence of 5% or greater and ABILIFY

incidence at least twice that for placebo) were: akathisia, restlessness, insomnia, constipation, fatigue, and blurred vision.

Less Common Adverse Reactions in Adult Patients with Major Depressive Disorder

Table 18 enumerates the pooled incidence, rounded to the nearest percent, of adverse reactions that occurred during acute therapy (up to 6 weeks), including only those adverse reactions that occurred in 2% or more of patients treated with adjunctive ABILIFY (doses ≥2 mg/day) and for which the incidence in patients treated with adjunctive ABILIFY was greater than the incidence in patients treated with adjunctive placebo in the combined dataset.

Table 18: Adverse Reactions in Short-Term, Placebo-Controlled Adjunctive Trials in Patients with Major Depressive Disorder

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

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

Dose-Related Adverse Reactions

Schizophrenia

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

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

Bipolar Mania

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

Autistic Disorder

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

Tourette's Disorder

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

Extrapyramidal Symptoms

Schizophrenia

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

Objectively collected data from those trials was collected on the Simpson Angus Rating Scale (for EPS), the Barnes Akathisia Scale (for akathisia), and the Assessments of Involuntary Movement Scales (for dyskinesias). In the adult schizophrenia trials, the objectively collected data did not show a difference between ABILIFY and placebo, with the exception of the Barnes Akathisia Scale (ABILIFY, 0.08; placebo, -0.05). In the pediatric (13 to 17 years) schizophrenia trial, the objectively collected data did not show a difference between ABILIFY and placebo, with the exception of the Simpson Angus Rating Scale (ABILIFY, 0.24; placebo, -0.29).

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

Bipolar Mania

In the short-term, placebo-controlled trials in bipolar mania in adults, the incidence of reported EPS-related events, excluding events related to akathisia, for monotherapy ABILIFY-treated patients was 16% vs. 8% for placebo and the incidence of akathisia-related events for monotherapy ABILIFY-treated patients was 13% vs. 4% for placebo. In the 6-week, placebo-controlled trial in bipolar mania for adjunctive therapy with lithium or valproate, the incidence of reported EPS-related events, excluding events related to akathisia for adjunctive ABILIFY-treated patients was 15% vs. 8% for adjunctive placebo and the incidence of akathisia-related events for adjunctive ABILIFY-treated patients was 19% vs. 5% for adjunctive placebo. In the short-term, placebo-controlled trial in bipolar mania in pediatric (10 to 17 years) patients, the incidence of reported EPS-related events, excluding events related to akathisia, for ABILIFY-treated patients was 26% vs. 5% for placebo and the incidence of akathisia-related events for ABILIFY-treated patients was 10% vs. 2% for placebo.

In the adult bipolar mania trials with monotherapy ABILIFY, the Simpson Angus Rating Scale and the Barnes Akathisia Scale showed a significant difference between aripiprazole

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

Major Depressive Disorder

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

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

Autistic Disorder

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

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

Tourette's Disorder

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

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

Dystonia

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

Laboratory Test Abnormalities

A between group comparison for 3-week to 6-week, placebo-controlled trials in adults or 4-week to 8-week, placebo-controlled trials in pediatric patients (6 to 17 years) revealed no medically important differences between the aripiprazole and placebo groups in the proportions of patients experiencing potentially clinically significant changes in routine serum chemistry, hematology, or urinalysis parameters. Similarly, there were no aripiprazole/placebo differences in the incidence of discontinuations for changes in serum chemistry, hematology, or urinalysis in adult or pediatric patients.

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

In a long-term (26-week), placebo-controlled trial there were no medically important differences between the aripiprazole and placebo patients in the mean change from baseline in prolactin, fasting glucose, triglyceride, HDL, LDL, or total cholesterol measurements. A similar profile was observed in long-term clinical trials of patients with bipolar disorder.

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 years) with schizophrenia, there was a slight difference in mean weight gain between aripiprazole and placebo patients (+0.13 kg vs. -0.83 kg, respectively) and also a difference in the proportion of patients meeting a

weight gain criterion of ≥7% of body weight [aripiprazole (5%) compared to placebo (1%)].

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

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

The mean weight gain with adjunctive aripiprazole was 1.7 kg vs. 0.4 kg with adjunctive placebo. The proportion of patients meeting a weight gain criterion of ≥7% of body weight was 5% with adjunctive aripiprazole compared to 1% with adjunctive placebo.

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

Table 19 provides the weight change results from a long-term (26-week), placebo-controlled study of aripiprazole in adults with schizophrenia, both mean change from baseline and proportions of patients meeting a weight gain criterion of ≥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 19: Weight Change Results Categorized by BMI at Baseline: Placebo Controlled Study in Schizoprenia, 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 20 provides the weight change results from a long-term (52-week) study of aripiprazole in adults with schizophrenia, both mean change from baseline and proportions of patients meeting a weight gain criterion of ≥7% of body weight relative to baseline, categorized by BMI at baseline:

Table 20: Weight Change Results Categorized by BMI at Baseline: Placebo Controlled Study in Schizoprenia, 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, bipolar mania, or major depressive disorder revealed no significant differences between oral aripiprazole and placebo in the proportion of patients experiencing potentially important changes in ECG parameters. Aripiprazole was associated with a median increase in heart rate of 2 beats per minute compared to no increase among placebo patients.

Additional Findings Observed in Clinical Trials

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

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

Other Adverse Reactions Observed During the Premarketing Evaluation of ABILIFY

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 13,543 adult patients. All events assessed as possible adverse drug reactions have been included with the exception of more commonly occurring events. In addition, medically/clinically meaningful adverse reactions, particularly those that are likely to be useful to the prescriber or that have

pharmacologic plausibility, have been included. Events already listed in other parts of *Adverse Reactions (6)*, or those considered in *Warning and Precautions (5)* or *Overdosage (10)* have been excluded. Although the reactions reported occurred during treatment with aripiprazole, they were not necessarily caused by it.

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

Adults - Oral Administration

Blood and Lymphatic System Disorders:

≥1/1000 patients and <1/100 patients - leukopenia, neutropenia, thrombocytopenia

Cardiac Disorders:

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

Eye Disorders:

≥1/1000 patients and <1/100 patients - photophobia, diplopia, eyelid edema, photopsia

Gastrointestinal Disorders:

≥1/1000 patients and <1/100 patients - gastroesophageal reflux disease, swollen tongue, esophagitis; *<1/1000 patients* – pancreatitis

General Disorders and Administration Site Conditions:

≥1/100 patients - asthenia, peripheral edema, chest pain; *≥1/1000 patients and <1/100 patients* - face edema, angioedema; *<1/1000 patients* - hypothermia

Hepatobiliary Disorders:

<1/1000 patients - hepatitis, jaundice

Immune System Disorders:

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

Injury, Poisoning, and Procedural Complications:

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

Investigations:

≥1/100 patients - weight decreased, creatine phosphokinase increased; *≥1/1000 patients and <1/100 patients* - hepatic enzyme increased, blood glucose increased, blood prolactin increased, blood urea increased, electrocardiogram QT prolonged, blood creatinine increased, blood bilirubin increased; *<1/1000 patients* - blood lactate

dehydrogenase increased, glycosylated hemoglobin increased, gamma-glutamyl transferase increased

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

Musculoskeletal and Connective Tissue Disorders:
≥1/1000 patients and <1/100 patients - muscle rigidity, muscular weakness, muscle tightness, mobility decreased; *<1/1000 patients* - rhabdomyolysis

Nervous System Disorders:
≥1/100 patients - coordination abnormal; *≥1/1000 patients and <1/100 patients* - speech disorder, parkinsonism, memory impairment, cogwheel rigidity, cerebrovascular accident, hypokinesia, tardive dyskinesia, hypotonia, myoclonus, hypertonia, akinesia, bradykinesia; *<1/1000 patients* - Grand Mal convulsion, choreoathetosis

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

Renal and Urinary Disorders:
≥1/1000 patients and <1/100 patients - urinary retention, polyuria, nocturia

Reproductive System and Breast Disorders:
≥1/1000 patients and <1/100 patients - menstruation irregular, erectile dysfunction, amenorrhea, breast pain; *<1/1000 patients* - gynaecomastia, priapism

Respiratory, Thoracic, and Mediastinal Disorders:
≥1/100 patients - nasal congestion, dyspnea, pneumonia aspiration

Skin and Subcutaneous Tissue Disorders:
≥1/100 patients - rash (including erythematous, exfoliative, generalized, macular, maculopapular, papular rash; acneiform, allergic, contact, exfoliative, seborrheic dermatitis, neurodermatitis, and drug eruption), hyperhydrosis; *≥1/1000 patients and <1/100 patients* - pruritus, photosensitivity reaction, alopecia, urticaria

Vascular Disorders:
≥1/100 patients - hypertension; *≥1/1000 patients and <1/100 patients* – hypotension

Pediatric Patients - Oral Administration

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

Gastrointestinal Disorders:
≥1/1000 patients and <1/100 patients - tongue dry, tongue spasm

Investigations:
≥1/100 patients - blood insulin increased

Nervous System Disorders:
≥1/1000 patients and <1/100 patients - sleep talking

Skin and Subcutaneous Tissue Disorders:
≥1/1000 patients and <1/100 patients - hirsutism

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of ABILIFY. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to establish a causal relationship to drug exposure: rare occurrences of allergic reaction (anaphylactic reaction, angioedema, laryngospasm, pruritus/urticaria, or oropharyngeal spasm), blood glucose fluctuation, blood prolactin decreased, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), hiccups, oculogyric crisis, pathological gambling and restless legs syndrome.

7 DRUG INTERACTIONS

7.1. Drugs Having Clinically Important Interactions with ABILIFY

Table 21 : Clinically Important Drug Interacrions with ABILIFY

Concomitant Drug Name or Drug Class	Clinical Rationale	Clinical Recommendation
Strong CYP3A4 Inhibitors (e.g., itraconazole, clarithromycin) or strong CYP2D6 inhibitors (e.g., quinidine, fluoxetine, paroxetine)	The concomitant use of ABILIFY with strong CYP3A4 or CYP2D6 inhibitors increased the exposure of aripiprazole compared to the use of ABILIFY alone *[see Clinical Pharmacology (12.3)]*	With concomitant use of ABILIFY with a strong CYP3A4 inhibitor or CYP2D6 inhibitor, reduce the ABILIFY dosage *[see Dosage and Administration (2.7)]*.
Strong CYP3A4 Inducers (e.g., carbamazepine, rifampin)	The concomitant use of ABILIFY and carbamazepine decreased the exposure of aripiprazole compared to the use of ABILIFY alone *[see Clinical Pharmacology (12.3)]*	With concomitant use of ABILIFY with a strong CYP3A4 inducer, consider increasing the ABILIFY dosage *[see Dosage and Administration (2.7)]*.
Antihypertensive Drugs	Due to its alpha adrenergic antagonism, aripiprazole has the potential to enhance	Monitor blood pressure and adjust dose accordingly *[see Warning and Precautions*

Concomitant Drug Name or Drug Class	Clinical Rationale	Clinical Recommendation
	the effect of certain antihypertensive agents	*(5.8)]*
Benzodiazepines (e.g., lorazepam)	The intensity of sedation was greater with the combination of oral aripiprazole and lorazepam as compared to that observed with aripiprazole alone. The orthostatic hypotension observed was greater with the combination as compared to that observed with lorazepam alone *[see Warnings and Precautions (5.8)]*	Monitor sedation and blood pressure. Adjust dose accordingly.
Central acting drugs or alcohol	Due to CNS effect of aripiprazole	Caution should be used when ABILIFY is taken in combination with other centrally-acting drugs or alcohol.

7.2 Drugs Having No Clinically Important Interactions with ABILIFY

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

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C: 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 body weights (10 mg/kg and 30 mg/kg), and increased incidences of hepatodiaphragmatic nodules and diaphragmatic hernia at 30 mg/kg (the other dose groups were not examined for these findings). A low incidence of diaphragmatic hernia was also seen in the fetuses exposed to 30 mg/kg. Postnatally, delayed vaginal opening was seen at 10 mg/kg and 30 mg/kg and impaired reproductive performance (decreased fertility rate, corpora lutea, implants, live fetuses, and increased post-implantation loss, likely mediated through effects on female offspring) was seen at 30 mg/kg. Some maternal toxicity was seen at 30 mg/kg; however, there was no evidence to suggest that these developmental effects were secondary to maternal toxicity.

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

Pregnant rabbits were treated with oral doses of 10 mg/kg/day, 30 mg/kg/day, and 100 mg/kg/day (2 times, 3 times, and 11 times human exposure at MRHD based on AUC and 6 times, 19 times, and 65 times the MRHD based on 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, 30 mg/kg/day) during the period of organogenesis, the highest dose, which caused pronounced maternal toxicity, resulted in decreased fetal weight, increased fetal abnormalities (primarily skeletal), and decreased fetal skeletal ossification. The fetal no-effect dose was 10 mg/kg, which produced 5 times the human exposure at the MRHD based on AUC and is 6 times the MRHD based on 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.

Non-teratogenic Effects

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. Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization. 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

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

8.4 Pediatric Use

Safety and effectiveness in pediatric patients with major depressive disorder have not been established.
The pharmacokinetics of aripiprazole and dehydro-aripiprazole in pediatric patients, 10 to 17 years of age, were similar to those in adults after correcting for the differences in body weight *[see Clinical Pharmacology (12.3)]*.

Schizophrenia

Safety and effectiveness in pediatric patients with schizophrenia were established in a 6-week, placebo-controlled clinical trial in 202 pediatric patients aged 13 to 17 years *[see Indication and Usage (1.1), Dosage and Administration (2.1), Adverse Reactions (6.2), and Clinical Studies (14.1)]*. Although maintenance efficacy in pediatric patients has not

been systematically evaluated, maintenance efficacy can be extrapolated from adult data along with comparisons of aripiprazole pharmacokinetic parameters in adult and pediatric patients.

Bipolar I Disorder

Safety and effectiveness in pediatric patients with bipolar mania were established in a 4-week, placebo-controlled clinical trial in 197 pediatric patients aged 10 to 17 years *[see Indication and Usage (1.2), Dosage and Administration (2.2), Adverse Reactions (6.2), and Clinical Studies (14.2)]*. Although maintenance efficacy in pediatric patients has not been systematically evaluated, maintenance efficacy can be extrapolated from adult data along with comparisons of aripiprazole pharmacokinetic parameters in adult and pediatric patients.

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

Irritability Associated with Autistic Disorder

Safety and effectiveness in pediatric patients demonstrating irritability associated with autistic disorder were established in two 8-week, placebo-controlled clinical trials in 212 pediatric patients aged 6 to 17 years *[see Indication and Usage (1.4), Dosage and Administration (2.4), Adverse Reactions (6.2), and Clinical Studies (14.4)]*.

Tourette's Disorder

Safety and effectiveness of aripiprazole in pediatric patients with Tourette's Disorder were established in one 8-week (aged 7 to 17) and one 10-week trial (aged 6 to 18) in 194 pediatric patients *[see Dosage and Administration (2.5), Adverse Reactions (6.1),and Clinical Studies (14.5)]*.

8.5 Geriatric Use

No dosage adjustment is recommended for elderly patients *[see also Boxed Warning and Warnings and Precautions (5.1), and Clinical Pharmacology (12.3)]*.

Of the 13,543 patients treated with oral ABILIFY in clinical trials, 1073 (8%) were ≥65 years old and 799 (6%) were ≥75 years old. Placebo-controlled studies of oral ABILIFY in schizophrenia, bipolar mania, or major depressive disorder did not include sufficient

numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

ABILIFY is not approved for the treatment of patients with psychosis associated with Alzheimer's disease *[see Boxed Warning and Warnings and Precautions (5.1)]*.

8.6 Hepatic and Renal Impairment

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

8.7 Other Specific Populations

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

9 DRUG ABUSE AND DEPENDENCE

9.1. Controlled Substance

ABILIFY is not a controlled substance.

9.2 Abuse

Aripiprazole has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of ABILIFY misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

9.3 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.

10 OVERDOSAGE

MedDRA terminology has been used to classify the adverse reactions.

10.1 Human Experience

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

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

10.2 Management of Overdosage

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

Charcoal: In the event of an overdose of ABILIFY, an early charcoal administration may be useful in partially preventing the absorption of aripiprazole. Administration of 50 g of activated charcoal, one hour after a single 15 mg oral dose of ABILIFY, decreased the mean AUC and Cmax of aripiprazole by 50%.

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

11 DESCRIPTION

Aripiprazole is a psychotropic drug that is available as ABILIFY® (aripiprazole) Tablets, ABILIFY DISCMELT® (aripiprazole) Orally Disintegrating Tablets, and ABILIFY® (aripiprazole) Oral Solution. 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 448.39. The chemical structure is:

ABILIFY Tablets are available in 5 mg, 10 mg, and 15 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, vanilla micron (flavor), 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 Orange Flavor.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of aripiprazole, as with other drugs having efficacy in schizophrenia, bipolar disorder, major depressive disorder, and irritability associated with autistic 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 (e.g., the orthostatic hypotension observed with aripiprazole may be explained by its antagonist activity at adrenergic alpha$_1$ receptors).

12.2 Pharmacodynamics

Aripiprazole exhibits high affinity for dopamine D_2 and D_3, serotonin 5-HT_{1A} and 5-HT_{2A} receptors (K_i values of 0.34 nM, 0.8 nM, 1.7 nM, and 3.4 nM, respectively), moderate affinity for dopamine D_4, serotonin 5-HT_{2C} and 5-HT_7, alpha$_1$-adrenergic and histamine H_1 receptors (K_i values of 44 nM, 15 nM, 39 nM, 57 nM, and 61 nM, respectively), and moderate affinity for the serotonin reuptake site (K_i=98 nM). Aripiprazole has no appreciable affinity for cholinergic muscarinic receptors (IC_{50}>1000 nM). Aripiprazole functions as a partial agonist at the dopamine D_2 and the serotonin 5-HT_{1A} receptors, and as an antagonist at serotonin 5-HT_{2A} receptor.

12.3 Pharmacokinetics

ABILIFY activity is presumably primarily due to the parent drug, aripiprazole, and to a lesser extent, to its major metabolite, dehydro-aripiprazole, which has been shown to have affinities for D_2 receptors similar to the parent drug and represents 40% of the parent drug exposure in plasma. The mean elimination half-lives are about 75 hours and 94 hours for aripiprazole and dehydro-aripiprazole, respectively. Steady-state concentrations are attained within 14 days of dosing for both active moieties. Aripiprazole accumulation is predictable from single-dose pharmacokinetics. At steady-state, the pharmacokinetics of aripiprazole 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 (2.7)]*. The single-dose pharmacokinetics of aripiprazole were linear and dose-proportional between the doses of 5 mg to 30 mg.

Distribution

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

Co-administration 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.

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

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

Mutagenesis

The mutagenic potential of aripiprazole was tested in the *in vitro* bacterial reverse-mutation assay, the *in vitro* bacterial DNA repair assay, the *in vitro* forward gene mutation

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

Impairment of Fertility

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

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

13.2 Animal Toxicology and/or Pharmacology

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

14 CLINICAL STUDIES

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

- Four short-term trials and one maintenance trial in adult patients and one short-term trial in adolescents (ages 13 to 17) with schizophrenia *[see Clinical Studies (14.1)]*

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

14.1 Schizophrenia

Adults

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

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

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

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

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

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

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

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

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

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

Pediatric Patients

The efficacy of ABILIFY (aripiprazole) in the treatment of schizophrenia in pediatric patients (13 to 17 years of age) was evaluated in one 6-week, placebo-controlled trial of outpatients who met DSM-IV criteria for schizophrenia and had a PANSS score ≥70 at baseline. In this trial (n=302) comparing two fixed doses of ABILIFY (10 or 30 mg/day) to placebo, ABILIFY was titrated starting from 2 mg/day to the target dose in 5 days in the 10 mg/day treatment arm and in 11 days in the 30 mg/day treatment arm. Both doses of ABILIFY were superior to placebo in the PANSS total score the primary outcome measure of the study. The 30 mg/day dosage was not shown to be more efficacious than the 10 mg/day dose. Although maintenance efficacy in pediatric patients has not been systematically evaluated, maintenance efficacy can be extrapolated from adult data along

with comparisons of aripiprazole pharmacokinetic parameters in adult and pediatric patients.

14.2 Bipolar Disorder

Acute Treatment of Manic and Mixed Episodes

Adults

Monotherapy

The efficacy of ABILIFY as monotherapy in the acute treatment of manic episodes was established in four 3-week, placebo-controlled trials in hospitalized patients who met the DSM-IV criteria for bipolar I disorder with manic or mixed episodes. These studies included patients with or without psychotic features and two of the studies also included patients with or without a rapid-cycling course.

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

In the four positive, 3-week, placebo-controlled trials (n=268; n=248; n=480; n=485) which evaluated ABILIFY in a range of 15 mg to 30 mg, once daily (with a starting dose of 15 mg/day in two studies and 30 mg/day in two studies), ABILIFY was superior to placebo in the reduction of Y-MRS total score and CGI-BP Severity of Illness score (mania). In the two studies with a starting dose of 15 mg/day, 48% and 44% of patients were on 15 mg/day at endpoint. In the two studies with a starting dose of 30 mg/day, 86% and 85% of patients were on 30 mg/day at endpoint.

Adjunctive therapy

The efficacy of adjunctive ABILIFY with concomitant lithium or valproate in the treatment of manic or mixed episodes was established in a 6-week, placebo-controlled study (n=384) with a 2-week lead-in mood stabilizer monotherapy phase in adult patients who met DSM-IV criteria for bipolar I disorder. This study included patients with manic or mixed episodes and with or without psychotic features.

Patients were initiated on open-label lithium (0.6 to 1.0 mEq/L) or valproate (50 to 125 µg/mL) at therapeutic serum levels, and remained on stable doses for 2 weeks. At the end of 2 weeks, patients demonstrating inadequate response (Y-MRS total score ≥16 and

≤25% improvement on the Y-MRS total score) to lithium or valproate were randomized to receive either aripiprazole (15 mg/day or an increase to 30 mg/day as early as day 7) or placebo as adjunctive therapy with open-label lithium or valproate. In the 6-week placebo-controlled phase, adjunctive ABILIFY starting at 15 mg/day with concomitant lithium or valproate (in a therapeutic range of 0.6 to 1.0 mEq/L or 50 to 125 µg/mL, respectively) was superior to lithium or valproate with adjunctive placebo in the reduction of the Y-MRS total score CGI-BP Severity of Illness score (mania). Seventy-one percent of the patients coadministered valproate and 62% of the patients coadministered lithium were on 15 mg/day at 6-week endpoint.

Pediatric Patients

The efficacy of ABILIFY in the treatment of bipolar I disorder in pediatric patients (10 to 17 years of age) was evaluated in one 4-week placebo-controlled trial (n=296) of outpatients who met DSM-IV criteria for bipolar I disorder manic or mixed episodes with or without psychotic features and had a Y-MRS score ≥20 at baseline. This double-blind, placebo-controlled trial compared two fixed doses of ABILIFY (10 or 30 mg/day) to placebo. The ABILIFY dose was started at 2 mg/day, which was titrated to 5 mg/day after 2 days, and to the target dose in 5 days in the 10 mg/day treatment arm and in 13 days in the 30 mg/day treatment arm. Both doses of ABILIFY were superior to placebo in change from baseline to week 4 on the Y-MRS total score

Maintenance Treatment of Bipolar I disorder

Monotherapy Maintenance Therapy

A maintenance trial was conducted in adult patients meeting DSM-IV criteria for bipolar I disorder with a recent manic or mixed episode who had been stabilized on open-label ABILIFY and who had maintained a clinical response for at least 6 weeks. The first phase of this trial was an open-label stabilization period in which inpatients and outpatients were clinically stabilized and then maintained on open-label ABILIFY (15 or 30 mg/day, with a starting dose of 30 mg/day) for at least 6 consecutive weeks. One hundred sixty-one outpatients were then randomized in a double-blind fashion, to either the same dose of ABILIFY they were on at the end of the stabilization and maintenance period or placebo and were then monitored for manic or depressive relapse. During the randomization phase, ABILIFY was superior to placebo on time to the number of combined affective relapses (manic plus depressive), the primary outcome measure for this study. A total of 55 mood events were observed during the double-blind treatment phase. Nineteen were from the ABILIFY group and 36 were from the placebo group.

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

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

Adjunctive Maintenance therapy

As adjunctive maintenance trial was conducted in adult patients meeting DSM-IV criteria for bipolar I disorder with a recent manic or mixed episode. Patients were initiated on open label lithium (0.6 to 1.0 mEq/L) or valproate (50 to 125 µg/mL) at therapeutic serum levels, and remained on stable doses for 2 weeks.

At the end of 2 weeks, patients demonstrating inadequate response (Y-MRS total score $\geq$16 and $\leq$35 % improvement on the Y-MRS total score) to lithium or valproate received ABIIFY with a starting dose of 15 mg/day with the option to increase to 30 mg or reduce to 10mg as early as day 4, as adjunctive therapy with open-label lithium or valproate.

Prior to randomization, patients on the combination of single-blind ABILIFY and lithium or valproate were required to maintain stability (Y-MRS and MADRS total scores $\leq$ 12) for 12 consecutive weeks.

Three hundred thirty-seven patients were then randomized in a double-blind fashion, to either the same dose of ABILIFY they were on at the end of the stabilization period or placebo plus lithium or valproate and were then monitored for manic, mixed, or depressive relapse for a maximum of 52 weeks.

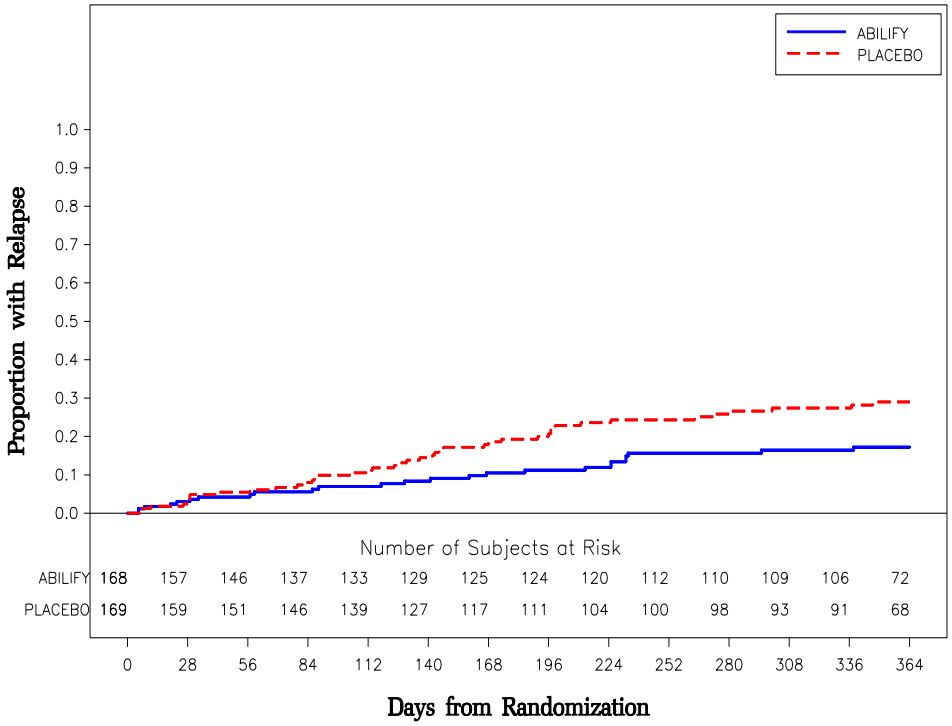
ABILIFY was superior to placebo on the primary endpoint, time from randomization to relapse to any mood event. A mood event was defined as hospitalization for a manic, mixed or depressive episode, study discontinuation due to lack of efficacy accompanied by Y-MRS score > 16 and/or a MADRS >16, or an SAE of worsening disease accompanied by Y-MRS score > 16 and/or a MADRS >16.

A total of 68 mood events were observed during the double-blind treatment phase. Twenty-five were from the ABILIFY group and 43 were from the placebo group.

The number of observed manic episodes in the ABILIFY group (7) were fewer than that in the placebo group (19), while the number of depressive episodes in the ABILIFY group (14) was similar to that in the placebo group (18).

The Kaplan-Meier curves of the time from randomization to relapse to any mood event during the 52-week double-blind treatment phase for ABILIFY and placebo groups are shown in Figure 1.

Figure 1 **Kaplan-Meier Estimation of Cumulative Proportion of Patients with Relapse to Any Mood Event (Bipolar Study 8)**



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

14.3 Adjunctive Treatment of Major Depressive Disorder

Adults

The efficacy of ABILIFY in the adjunctive treatment of major depressive disorder (MDD) was demonstrated in two short-term (6-week), placebo-controlled trials of adult patients meeting DSM-IV criteria for MDD who had had an inadequate response to prior antidepressant therapy (1 to 3 courses) in the current episode and who had also demonstrated an inadequate response to 8 weeks of prospective antidepressant therapy (paroxetine controlled-release, venlafaxine extended-release, fluoxetine, escitalopram, or sertraline). Inadequate response for prospective treatment was defined as less than 50% improvement on the 17-item version of the Hamilton Depression Rating Scale (HAMD17), minimal HAMD17 score of 14, and a Clinical Global Impressions Improvement rating of no better than minimal improvement. Inadequate response to prior treatment was defined as less than 50% improvement as perceived by the patient after a minimum of 6 weeks of antidepressant therapy at or above the minimal effective dose.

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

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

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

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

14.4 Irritability Associated with Autistic Disorder

Pediatric Patients

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

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

The results of these trials are as follows:

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

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

14.5 Tourette's Disorder

Pediatric Patients

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

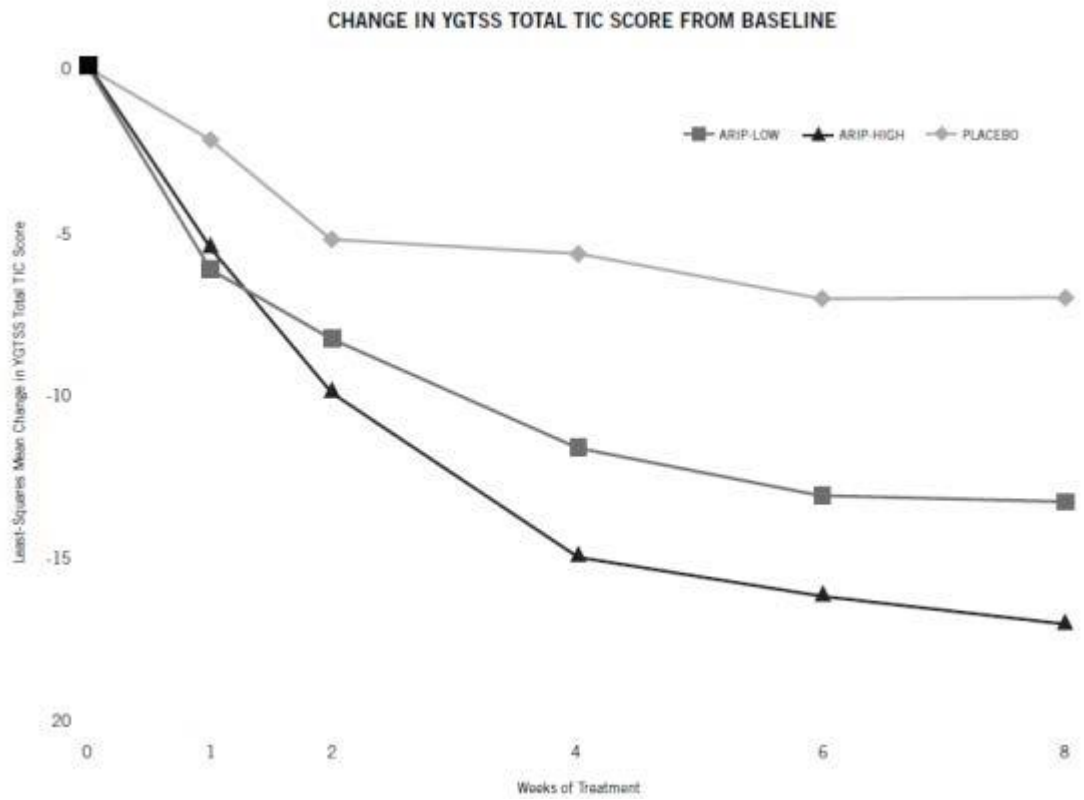
The primary outcome measure in both trials was the change from baseline to endpoint in the TTS of the YGTSS. Ratings for the TTS are made along 5 different dimensions on a scale of 0 to 5 for motor and vocal tics each. Summation of these 10 scores provides a TTS (i.e., 0-50).

The results of these trials are as follows:

In the 8-week, placebo-controlled, fixed-dose trial, children and adolescents with Tourette's disorder (n=133), aged 7 to 17 years, were randomized 1:1:1 to low dose

ABILIFY, high dose ABILIFY, or placebo. The target doses for the low and high dose ABILIFY groups were based on weight. Patients < 50 kg in the low dose ABILIFY group started at 2 mg per day with a target dose of 5 mg per day after 2 days. Patients ≥ 50 kg in the low dose ABILIFY group, started at 2 mg per day increased to 5 mg per day after 2 days, with a subsequent increase to a target dose of 10 mg per day at day 7. Patients <50 kg in the high dose ABILIFY group started at 2 mg per day increased to 5 mg per day after 2 days, with a subsequent increase to a target dose of 10 mg per day at day 7. Patients ≥ 50 kg in the high dose ABILIFY group, started at 2 mg per day increased to 5 mg per day after 2 days, with a subsequent increase to a dose of 10 mg per day at day 7 and were allowed weekly increases of 5 mg per day up to a target dose 20 mg per day at Day 21. ABILIFY (both high and low dose groups) demonstrated statistically significantly improved scores on the YGTSS TTS (Study 1 in Table 22) and on the CGI-TS scale compared with placebo. The estimated improvements on the YGTSS TTS over the course of the study are displayed in Figure 2.

Figure 2: Least Square Means of Change from Baseline in YGTSS TTS by Week (Tourette's Disorder Study 1)



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

YGTSS TTS scale compared with placebo (Study 2 in Table 22). The mean daily dose of ABILIFY at the end of 10-week treatment was 6.54 mg/day.

Table 22: Tourette's Disorder Studies (Pediatric)

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

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

15 HOW SUPPLIED/STORAGE AND HANDLING

15.1 How Supplied

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

The 5-mg ABILIFY® tablets are blue, modified rectangular tablets, debossed on one side with "A-007" and "5".
Boxes of 1 blister of 10 tablets Reg.No DKI0809700110D1

The 10-mg ABILIFY® tablets are pink, modified rectangular tablets, debossed on one side with "A-008" and "10".
Boxes of 1 blister of 10 tablets Reg.No DKI0409700110A1

The 15-mg ABILIFY® tablets are yellow, round tablets, debossed on one side with "A-009" and "15".
Boxes of 1 blister of 10 tablets Reg.No DKI0409700110B1

ABILIFY® (aripiprazole) Oral Solution (1 mg/mL) is supplied in child-resistant bottles along with a calibrated oral measuring cup and pipette. ABILIFY oral solution is available as follows: 150 mL bottle.

Boxes of 1 bottle of 150 mL Reg.No DKI1509700735A1

The 10-mg ABILIFY DISCMELT® Orally Disintegrating Tablets are pink, round tablets with scattered specks, debossed with "A" over 640" on one side and "10" debossed on the other.
Boxes of 1 blister of 10 tablets Reg.No DKI1509700681A1

The 15-mg ABILIFY DISCMELT® Orally Disintegrating Tablets are yellow, round tablets with scattered specks, debossed with "A" over 641" on one side and "15" debossed on the other.
Boxes of 1 blister of 10 tablets Reg.No DKI1509700681B1

15.2 Storage

Tablet 5mg, 10mg, 15mg
Store below 30ºC.

Orally Disintegrating Tablets 10 mg & 15 mg
Store below 30ºC.

Oral Solution
Store below 30°C. Opened bottles of ABILIFY oral solution can be used for up to 6 months after opening, but not beyond the expiration date on the bottle. The bottle and its contents should be discarded after the expiration date.

Tablets 5 mg, 10 mg & 15 mg manufactured by:
Korea Otsuka Pharmaceutical Co., Ltd.
27, Jeyakgongdan 3-gil, Hyangnam-eup, Hwaseong-si, Gyeonggi-do, 18622, Korea

Orally disintegrating tablets 10 mg & 15 mg manufactured by:
Korea Otsuka Pharmaceutical Co., Ltd
27, Jeyakgongdan 3-gil, Hyangnam-eup, Hwaseong-si, Gyeonggi-do, 18622 Korea

Oral Solution Bottle 150 ml manufactured by:
Korea Otsuka Pharmaceutical Co., Ltd
27, Jeyakgongdan 3-gil, Hyangnam-eup, Hwaseong-si, Gyeonggi-do, 18622 Korea

HARUS DENGAN RESEP DOKTER

Otsuka

Imported by:
PT Otsuka Indonesia
Jl. Sumber Waras. No.25
Lawang, Malang 65216 Indonesia

Otsuka

Under Authorization of:
Otsuka Pharmaceutical Co., Ltd., Japan

INFORMASI PRODUK UNTUK PASIEN
ABILIFY® TABLET
ABILIFY DISCMELT®
ABILIFY® CAIRAN ORAL

Bentuk sediaan : Tablet 5 mg
Tablet 10 mg
Tablet 15 mg
DISCMELT 10 mg
DISCMELT 15 mg
Cairan Oral (1 mg/ml)

Pemerian obat : ABILIFY 5 mg : Tablet biru persegi panjang, dengan tanda "A-007" dan "5" pada salah satu sisi..
ABILIFY 10 mg : Tablet pink persegi panjang, dengan tanda"A-008" and "10" pada salah satu sisi.
ABILIFY 15 mg : Tablet kuning bulat, dengan tanda "A-009" dan "15" pada salah satu sisi
ABILIFY DISCMELT 10 mg : Tablet pink bulat, dengan tanda "A-640" pada salah satu sisi dan "10" pada sisi yang lain.
ABILIFY DISCMELT 15 mg : Tablet kuning bulat, dengan tanda "A-641" pada salah satu sisi dan "15" pada sisi lain.
ABILIFY Cairan Oral : tersedia dalam *child-resistant bottle* beserta sebuah gelas takar dosis dan pipet karet terkalibrasi. ABILIFY cairan oral tersedia dalam botol 150 ml

Kekuatan : ABILIFY Tablet 5 mg mengandung Aripiprazole 5 mg
ABILIFY Tablet 10 mg mengandung Aripiprazole 10 mg
ABILIFY Tablet 15 mg mengandung Aripiprazole 15 mg
ABILIFY Discmelt tablet 10 mg mengandung Aripiprazole 10 mg
ABILIFY Discmelt tablet 15 mg mengandung Aripiprazole 15 mg
ABILIFY Cairan Oral mengandung Aripiprazole 1 mg/ml

Untuk apa ABILIFY dikonsumsi?

ABILIFY Tablet, Discmelt, Cairan Oral adalah obat dengan resep dokter yang dikonsumsi untuk mengobati:

- skizofrenia pada penderita yang berusia 13 tahun atau lebih.
- gangguan Bipolar I pada penderita yang berusia 10 tahun atau lebih, termasuk :
  * episode manik atau campuran yang terjadi bersama dengan gangguan bipolar I.
  * episode manik atau campuran yang terjadi bersama dengan gangguan bipolar I. ketika mengonsumsi obat Lithium atau Valproate.
  * pengobatan jangka panjang untuk gangguan bipolar I,
- gangguan depresi mayor pada orang dewasa, sebagai obat tambahan terhadap obat antidepresan ketika Anda merasa tidak lebih baik dengan obat antidepresan saja.

- iritabilitas pada gangguan autistik pada anak dan remaja yang berusia 6 sampai 17 tahun.
- Gangguan Tourette pada anak dan remaja yang berusia 6 sampai 18 tahun.

Belum diketahui apakah ABILIFY aman dan efektif untuk anak :
- Dibawah usia 13 tahun untuk pengobatan skizofrenia
- Dibawah usia 10 tahun untuk pengobatan gangguan bipolar I
- Dibawah usia 6 tahun untuk pengobatan irritabilitas yang berhubungan dengan gangguan autis
- Di bawah usia 6 tahun untuk gangguan Tourette.

Bagaimana cara mengonsumsi ABILIFY?
- Minum ABILIFY sesuai saran dokter. Jangan merubah dosis atau menghentikan ABILIFY atas inisiatif sendiri .
- ABILIFY dapat diminum dalam keadaan perut kosong atau bersama makanan.
- ABILIFY tablet harus ditelan seluruhnya.
- Jika mengonsumsi ABILIFY Discmelt tablet, gunakan dengan cara :
  - Tidak membuka kemasan blister sampai waktu akan minum Discmelt tablet.
  - Untuk mengeluarkan satu Discmelt tablet, buka kemasan dan kelupas lapisan kemasan untuk mengeluarkan tablet.
  - Jangan menekan tablet dalam kemasan blister karena akan merusak tablet.
  - Gunakan tangan dalam keadaan kering saat membuka blister, ambil dan letakkan Discmelt tablet ke dalam lidah.
  - Discmelt tablet langsung larut dengan adanya air liur. Dianjurkan untuk mengonsumsi ABILIFY Discmelt tablet tanpa air. Namun bila dibutuhkan dapat dikonsumsi dengan air.
  - Jangan mencoba untuk membelah Discmelt tablet.

Apa yang harus dilakukan bila lupa mengonsumsi obat?

Jika lupa mengonsumsi obat, saat ingat, segera konsumsi obat. Jika sudah tiba waktu untuk mengonsumsi obat selanjutnya, maka abaikan mengonsumsi obat yang terlupa dan mengonsumsi obat pada waktunya.
Jangan konsumsi obat dua kali dosis ABILIFY pada waktu yang sama.

Pada keadaan apa Anda tidak diperbolehkan mengonsumsi obat ini ?

Jangan mengonsumsi ABILIFY jika Anda alergi terhadap Aripiprazole atau bahan tambahan pada ABILIFY.

Apa yang harus saya informasikan pada dokter sebelum mengonsumsi ABILIFY?
Sebelum mengonsumsi ABILIFY, beritahukan dokter Anda bila Anda memiliki atau pernah memiliki:
- Diabetes atau kadar gula darah tinggi pada Anda atau keluarga Anda, dokter harus memeriksa kadar gula darah Anda sebelum dan selama pengobatan.
- Kejang

- Tekanan darah tinggi atau tekanan darah rendah
- Masalah jantung atau stroke
- Hamil atau sedang merencanakan kehamilan. Tidak diketahui apakah ABILIFY dapat menyebabkan kondisi yang membahayakan bayi yang dikandung.
- Menyusui atau sedang merencanakan untuk menyusui. ABILIFY dapat masuk ke dalam air susu dan dapat membahayakan bayi Anda. Bicaralah dengan dokter Anda mengenai cara terbaik untuk memberi makan bayi Anda jika Anda mengonsumsi ABILIFY.
- Jumlah sel darah putih yang rendah.
- Phenylketonuria. ABILIFY Discmelt tablet mengandung phenylalanine.
- Kondisi pengobatan lainnya.

Informasi penting apa yang harus saya ketahui tentang ABILIFY?

Telah dilaporkan efek samping yang serius dari ABILIFY termasuk:

- **Peningkatan risiko kematian pada pasien lanjut usia dengan psikosis yang berkaitan dengan demensia.**
  Obat ABILIFY dapat meningkatkan risiko kematian pada lanjut usia yang sudah tidak berhubungan dengan kenyataan (psikosis) karena bingung dan hilangnya daya ingat (demensia),
  ABILIFY tidak disetujui untuk pengobatan pasien psikosis yang berkaitan dengan demensia.

- Risiko keinginan/melakukan bunuh diri: Obat antidepresan, depresi dan kelainan jiwa lainnya yang serius, dan keinginan/tindakan bunuh diri:

  1. **Obat Antidepresan dapat meningkatkan keinginan atau tindakan bunuh diri pada anak, remaja dan orang dewasa dalam beberapa bulan pertama pengobatan.**

  2. **Depresi dan kelainan jiwa lain yang serius adalah penyebab paling penting dari keinginan/ tindakan bunuh diri. Beberapa orang mempunyai risiko tinggi untuk bunuh diri.** Termasuk orang yang memiliki (atau mempunyai riwayat keluarga) penyakit bipolar (juga disebut penyakit manik-depresif) atau pikiran keinginan atau tindakan bunuh diri.

  3. **Bagaimana saya dapat mengawasi dan mencoba mencegah keinginan dan tindakan bunuh diri pada diri saya atau anggota keluarga saya?**

     - Beri perhatian penuh pada tiap perubahan, terutama perubahan tiba-tiba pada mood/sikap, kelakuan, pikiran atau perasaan. Terutama pada saat pengobatan antidepresan dimulai atau ketika dosis diubah.
     - Segera hubungi dokter bila terjadi perubahan tiba tiba atau perubahan mood/sikap , tingkah laku, pikiran atau perasaan.
     - Simpan semua berkas kunjungan ke dokter. Bila perlu hubungi dokter di luar jadwal kunjungan, terutama jika Anda memiliki kekhawatiran tentang gejala yang ada.

Segera hubungi dokter jika Anda atau anggota keluarga Anda mempunyai gejala-gejala di

bawah ini, terutama jika gejala tersebut baru, memburuk, atau membuat Anda khawatir seperti:

- pikiran hendak bunuh diri atau meninggal
- mencoba bunuh diri
- depresi atau memburuknya depresi
- cemas atau memburuknya rasa cemas
- merasa tidak tenang atau gelisah
- merasa panik
- sukar tidur (insomnia)
- menjadi iritabel atau makin memburuk
- berperilaku agresif, menjadi pemarah atau kasar
- melakukan hal yang berbahaya
- peningkatan ekstrim pada aktifitas dan berbicara (mania)
- perubahan tingkah laku/mood yang tidak biasa lainnya

Hal lain apa yang harus saya ketahui tentang obat antidepresan?

- **Jangan pernah menghentikan obat antidepresan tanpa terlebih dahulu berbicara pada dokter.** Menghentikan obat antidepresan secara tiba-tiba dapat menyebabkan gejala lain.

  - **Antidepresan adalah obat yang dikonsumsi untuk mengobati depresi dan penyakit lainnya.** Sangatlah penting untuk mendiskusikan semua risiko dari pengobatan depresi dan juga risiko bila tidak mengobatinya. Pasien dan keluarganya atau orang yang merawat harus mendiskusikan semua pilihan pengobatan dengan dokter, tidak hanya mengenai mengonsumsi obat antidepresan saja.

- **Efek samping lainnya dari obat antidepresan.** Bicarakan dengan dokter mengenai efek samping dari obat yang diresepkan untuk Anda atau anggota keluarga Anda.

  - **Obat Antidepresan dapat berinteraksi dengan obat lain.** Pahami semua obat yang dikonsumsi oleh Anda atau anggota keluarga Anda. Simpan daftar semua obat yang dikonsumsi, perlihatkan daftar tersebut kepada dokter. Jangan memulai obat baru tanpa pemeriksaan dokter terlebih dahulu.

- **Tidak semua obat antidepresan yang diresepkan untuk anak telah disetujui FDA untuk dikonsumsi pada anak.** Bicarakan dengan dokter yang merawat anak Anda untuk memperoleh informasi lebih lanjut**.**

Makanan dan obat apa yang harus saya hindari selama pengobatan dengan ABILIFY ?

- **Beri tahu dokter Anda mengenai semua obat yang Anda konsumsi atau baru saja Anda konsumsi,** termasuk semua obat resep dokter, obat tanpa resep dokter, suplemen herbal dan vitamin.

ABILIFY dan obat lainnya dapat saling berpengaruh satu sama lain yang mengakibatkan efek samping yang serius. ABILIFY dapat mempengaruhi mekanisme

kerja obat lain dan juga sebaliknya.

Dokter Anda dapat menjelaskan pada Anda jika ABILIFY aman dikonsumsi bersama obat Anda yang lain. Jangan memulai atau mengakhiri obat lain selama mengonsumsi ABILIFY tanpa memberi tahu dokter Anda terlebih dahulu.
Kenali obat yang Anda konsumsi. Simpan daftar obat-obat Anda untuk diperlihatkan pada dokter dan apoteker ketika Anda mendapat obat baru.

Apa yang harus saya hindari selama mengonsumsi ABILIFY?

- Jangan mengendarai mobil, mengoperasikan mesin berat atau aktifitas yang membahayakan sampai Anda tahu bagaimana ABILIFY mempengaruhi Anda. ABILIFY menyebabkan Anda mengantuk.
- Hindari mengalami dehidrasi atau terlalu panas.
  Jangan berolahraga berlebihan.
  Pada cuaca panas, jika memungkinkan berada di tempat sejuk.
  Hindari matahari. Jangan memakai pakaian yang terlalu banyak atau tebal.
  Minum air putih yang banyak.

Apakah ABILIFY dapat dikonsumsi pada wanita hamil dan menyusui?

- Kehamilan atau rencana untuk hamil. Tidak diketahui apakah ABILIFY akan membahayakan bayi yang ada dalam kandungan.
- Menyusui atau merencanakan untuk menyusui. ABILIFY dapat masuk ke dalam air susu dan dapat membahayakan bayi Anda. Bicaralah dengan dokter Anda mengenai cara terbaik untuk memberi makan bayi Anda jika Anda menerima ABILIFY.

Apakah selama mengonsumsi ABILIFY boleh mengendarai mobil atau mengoperasikan mesin?

Tidak boleh mengemudi, mengoperasikan mesin berat atau aktifitas lain yang membahayakan sampai Anda mengetahui apakah ABILIFY akan mempengaruhi Anda. ABILIFY dapat membuat Anda mengantuk.

Apakah efek samping yang mungkin terjadi saat mengonsumsi ABILIFY:

- **Lihat Informasi penting yang harus diketahui tentang ABILIFY**

- **Stroke pada lanjut usia (masalah pada *cardiovascular*) yang dapat menyebabkan kematian**
- ***Neuroleptic malignant syndrome* (NMS):** Segera hubungi dokter Anda jika Anda mengalami beberapa atau semua gejala gejala berikut ini : demam tinggi, otot kaku, kebingungan, berkeringat, perubahan denyut nadi, detak jantung, dan tekanan darah. Ini mungkin gejala dari kondisi langka dan serius yang dapat menyebabkan kematian. Segera hubungi dokter jika mengalami gejala-gejala tersebut .
- **Gerakan badan tidak terkontrol (*Tardive dyskinesia*)**: Hubungi dokter Anda

untuk setiap gerakan tidak terkontrol pada wajah, lidah atau anggota tubuh lainnya. Ini mungkin menunjukkan kondisi yang serius. *Tardive dyskinesia* mungkin tidak segera sembuh bahkan jika Anda berhenti mengonsumsi ABILIFY. *Tardive dyskinesia* dapat juga muncul pada saat Anda telah berhenti mengonsumsi ABILIFY.

- **Masalah pada metabolisme seperti**

- **Kadar gula darah tinggi (hiperglikemia) :** Pada beberapa orang yang mengonsumsi ABILIFY dapat terjadi peningkatan kadar gula. Peningkatan kadar gula darah secara ekstrim dapat menyebabkan koma atau kematian.
  Jika Anda diabetes atau memiliki faktor risiko diabetes (seperti berat badan berlebih atau mempunyai anggota keluarga diabetes), dokter Anda harus memeriksa kadar gula darah Anda sebelum Anda memulai pengobatan dengan ABILIFY dan selama pengobatan.

  Hubungi dokter Anda jika Anda mengalami gejala karena tingginya kadar gula darah selama mengonsumsi ABILIFY:
  - merasa sangat haus
  - sering kencing lebih dari biasanya .
  - merasa sangat lapar
  - merasa lemas atau lelah
  - sakit pada lambung
  - merasa bingung, atau nafas berbau

- **Peningkatan kadar lemak (kolesterol dan trigliserida) dalam darah**

- **Peningkatan berat badan:** Anda dan dokter Anda harus memeriksa berat badan Anda secara teratur.

- **Desakan yang luar biasa**
  Beberapa orang yang mengonsumsi ABILIFY, dapat mengalami desakan yang tidak biasa seperti berjudi, makan berlebihan atau makan yang tidak dapat Anda kendalikan (kompulsif), belanja secara berlebihan dan desakan seksual
  Jika Anda atau anggota keluarga Anda memperhatikan bahwa Anda mengalami desakan atau perilaku yang tidak biasa, konsultasikan kepada tenaga kesehatan.

- **Hipotensi Ortostatik (penurunan tekanan darah):** kepala terasa ringan atau merasa akan pingsan ketika bangkit terlalu cepat dari posisi duduk atau berbaring.

- **Terjatuh.** ABILIFY dapat menyebabkan kantuk dan pusing, dapat menyebabkan penurunan tekanan darah ketika merubah posisi tubuh dan dapat memperlambat kemampuan berpikir dan kemampuan motorik yang dapat menyebabkan terjatuh sehingga mengalami patah tulang atau cedera lainnya.

- **Jumlah sel darah putih yang rendah.**

- **Seizures (kejang)**

- **Masalah dengan kontrol suhu tubuh Anda terutama saat Anda banyak**

berolahraga atau berada di aera yang sangat panas.

Sangat penting untuk banyak minum untuk menghindari dehidrasi. Lihat **"Apa yang harus saya hindari selama mengonsumsi ABILIFY?"**

- **Sukar menelan:** dapat menyebabkan aspirasi dan tersedak

Efek samping umum ABILIFY pada orang dewasa termasuk:

- mual
- muntah
- konstipasi
- sakit kepala
- penglihatan kabur
- penyakit pada saluran napas bagian atas
- pusing
- cemas
- sulit tidur
- gelisah
- rasa gelisah/ingin bergerak (akathisia)

Efek samping yang umumnya terjadi pada konsumsi ABILIFY pada anak, termasuk:

- merasa mengantuk
- sakit kepala
- muntah
- kelelahan
- peningkatan atau penurunan nafsu makan
- peningkatan jumlah air liur
- sulit tidur
- mual
- hidung tersumbat
- penambahan berat badan
- gerakan tidak terkontrol seperti gelisah, tremor
- otot kaku

Ini semua bukan keseluruhan efek samping ABILIFY. Untuk informasi tambahan, tanyakan dokter Anda atau apoteker.

Hubungi dokter Anda untuk saran pengobatan tentang efek samping.

Apa gejala dan tanda kelebihan dosis ABILIFY?

Gejala dan tanda kelebihan dosis ABILIFY (ABILIFY saja atau kombinasi dengan obat lainnya) meliputi: mual, mengantuk, tremor, asidosis, agresif, peningkatan kadar aspartat aminotransferase, fibrilasi atrium, bradikardi, koma, bingung, kejang, peningkatan kadar kreatin phosphokinase dalam darah, tingkat kesadaran menurun, hipertensi, hipokalemia, hipotensi, lesu, hilang kesadaran, perpanjangan QRS kompleks, perpanjangan QT, aspirasi pneumonia, henti nafas, status epileptikus, dan takikardi.

Apa yang terjadi jika saya kelebihan dosis ABILIFY?

Jika terjadi kelebihan dosis ABILIFY, hubungi dokter Anda atau pergi ke rumah sakit terdekat.

Bagaimana cara penyimpanan ABILIFY?

Tablet 5 mg, 10 mg dan 15 mg: Simpan pada suhu dibawah 30°C.

DISCMELT 10 and 15 mg : Simpan pada suhu dibawah 30°C

Cairan Oral: Simpan pada suhu dibawah 30°C . ABILIFY cairan oral yang telah dibuka masih dapat dikonsumsi sampai 6 bulan selama belum kadaluwarsa.
Botol dan isinya harus dibuang setelah tanggal kadaluarsa

Jauhkan ABILIFY dan obat lainnya dari jangkauan anak-anak.

Komposisi ABILIFY adalah :

Zat Aktif : Aripiprazole

Zat tambahan :
ABILIFY Tablet : cornstarch, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, and microcrystalline cellulose. Pewarna mengandung ferric oxide (yellow or red) dan FD&C Blue No. 2 Aluminum Lake.

ABILIFY Discmelt : acesulfame potassium, aspartame, calcium silicate, croscarmellose sodium, crospovidone, vanilla micron (flavor), magnesium stearate, microcrystalline cellulose, silicon dioxide, tartaric acid, and xylitol. Pewarna mengandung ferric oxide (yellow or red) dan FD&C Blue No. 2 Aluminum Lake.

ABILIFY Cairan Oral : disodium edetate, fructose, glycerin, dl-lactic acid, methylparaben, propylene glycol, propylparaben, sodium hydroxide, sucrose, and purified water. Cairan oral ditambahkan dengan perisa rasa jeruk (*Orange Flavor*).

Tablet 5 mg ,10 mg and 15 mg :
Diproduksi oleh :
Korea Otsuka Pharmaceutical Co., Ltd
27, Jeyakgongdan 3-gil, Hyangnam-eup, Hwaseong-si, Gyeonggi-do, 18622 Korea

DISCMELT 10 mg and 15 mg :
Diproduksi oleh :
Korea Otsuka Pharmaceutical Co., Ltd
27, Jeyakgongdan 3-gil, Hyangnam-eup, Hwaseong-si, Gyeonggi-do, 18622 Korea

Cairan Oral
Diproduksi oleh :
Korea Otsuka Pharmaceutical Co., Ltd
27, Jeyakgongdan 3-gil, Hyangnam-eup, Hwaseong-si, Gyeonggi-do, 18622 Korea

HARUS DENGAN RESEP DOKTER

Diimpor oleh :
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Jl Sumber Waras No. 25
Lawang, Malang 65216 Indonesia

Dibawah otorisasi dari:
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