ABILIFY®

(aripiprazole)

Tablets
Oral Solution

WARNING

Increased Mortality in Elderly Patients with Dementia-Related Psychosis and Suicidal Thoughts and Behaviours with Antidepressant Drugs

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. ABILIFY is not approved for the treatment of patients with dementia-related psychosis [*see WARNINGS AND PRECAUTIONS (4.1)*].

Antidepressants increased the risk of suicidal thoughts and behaviour 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 antidepressant use in patients over age 24 years; there was a reduction in risk with antidepressant use in patients aged 65 years and older [*see WARNINGS AND PRECAUTIONS (4.3)*].

In patients of all ages who are started on antidepressant therapy, monitor closely for worsening, and for emergence of suicidal thoughts and behaviours. Advice families and caregivers of the need for close observation and communication with the prescriber [*see WARNINGS AND PRECAUTIONS (4.3)*].

1. INDICATIONS AND USAGE

Schizophrenia

ABILIFY is indicated for the treatment of schizophrenia. The efficacy of ABILIFY in the treatment of

schizophrenia was established in four short-term (4- and 6-week) controlled trials in adults and one 6-week trial in paediatrics (13 to 17 years). Maintenance efficacy was demonstrated in one trial in adults and can be extrapolated to paediatrics *[see CLINICAL STUDIES (13.1)]*. The physician who elects to use ABILIFY for extended periods should periodically re-evaluate the long- term usefulness of the drug for the individual patient *[see DOSAGE AND ADMINISTRATION (2)]*.

Bipolar I Disorder

ABILIFY is indicated for the treatment of acute manic and mixed episodes associated with Bipolar I Disorder and for maintaining stability or preventing recurrence, as monotherapy in adults and in adolescents aged 13 years and older, and as an adjunct to lithium or valproate in adults.

The efficacy of ABILIFY as monotherapy was established in four 3-week monotherapy trials in adults and one 4-week monotherapy trial in paediatric patients. Efficacy as adjunctive therapy was established in one 6-week adjunctive trial in adults *[see CLINICAL STUDIES (13.2)]*.

Maintenance efficacy was demonstrated in one monotherapy maintenance trial and in one adjunctive maintenance trial in adults *[see CLINICAL STUDIES (13.2)]*. Physicians who elect to use ABILIFY for extended periods, should periodically re-evaluate the long-term usefulness of the drug for the individual patient *[see DOSAGE AND ADMINISTRATION (2)]*.

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 three 6-week trials in adults with MDD who had an inadequate response to antidepressant therapy during the current episode *[see CLINICAL STUDIES (13.3)]*.

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 paediatric 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 (13.4)]*.

The efficacy of ABILIFY for the maintenance treatment of irritability associated with autistic disorder was not established.

Tourette's Disorder

ABILIFY is indicated for the treatment of Tourette's disorder. Efficacy was established in one 8-week

(aged 7 to 17 years) and one 10-week (aged 6 to 18 years) placebo-controlled trial in paediatric patients with Tourette's disorder *[see CLINICAL STUDIES (13.5)]*.

2. DOSAGE AND ADMINISTRATION

2.1 Schizophrenia

Adults

Usual Dose

The recommended starting and target dose for ABILIFY is 10 or 15 mg/day administered on a once-a-day schedule without regard to meals. ABILIFY has been systematically evaluated and shown to be effective in a dose range of 10 to 30 mg/day; 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 (13.1)]*.

Maintenance Therapy

While there is no body of evidence available to answer the question of how long a patient treated with aripiprazole should remain on it, systematic evaluation of patients with schizophrenia who had been symptomatically stable on other antipsychotic medication, for periods of 3 months or longer, were discontinued from those medications, and were then administered ABILIFY 15 mg/day and observed for relapse during a period of up to 26 weeks, demonstrated a benefit of such maintenance treatment *[see CLINICAL STUDIES (13.1)]*. Patients should be periodically reassessed to determine the need for maintenance treatment.

Adolescents

Usual Dose

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 30mg. 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 and was associated with a higher incidence of significant adverse reactions including extrapyramidal disorder, somnolence and tremor *[see ADVERSE REACTIONS (5.1)]*. ABILIFY can be administered without regard to meals *[see CLINICAL STUDIES (13.1)]*.

Maintenance Therapy

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 paediatric 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 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.

Adolescents

The recommended starting dose in adolescent patients 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. Subsequent dose increases, if needed, should be administered in 5 mg/day increments. ABILIFY can be given without regard to meals. Enhanced efficacy at doses higher than a daily dose of 10 mg has not been demonstrated, and a daily dose of 30 mg is associated with a substantially higher incidence of significant adverse reactions including extrapyramidal disorder, somnolence, akathisia and salivary hypersecretion. Doses higher than 10 mg/day should therefore only be used in exceptional cases and with close clinical monitoring *[see WARNINGS AND PRECAUTIONS (4.6), ADVERSE REACTIONS (5.1), and CLINICAL STUDIES (13.2)]*. Younger patients are at increased risk of experiencing adverse events associated with aripiprazole. Therefore, ABILIFY is not recommended for use in patients below 13 years of age *[see ADVERSE REACTIONS (5.1) and CLINICAL STUDIES (13.2)]*.

Maintenance Therapy

The recommended dose for maintenance treatment is the same dose needed to stabilize patients during acute treatment, both for adult and paediatric patients. Systematic evaluation of adult patients with Bipolar I Disorder experiencing a manic or mixed episode, who had been symptomatically stable on

ABILIFY Tablets (15 mg/day or 30 mg/day with a starting dose of 30 mg/day) for 6 consecutive weeks and then randomized to ABILIFY Tablets (15 mg/day or 30 mg/day) or placebo for at least 6 months and up to an additional 17 months of observation for relapse, demonstrated a benefit of such maintenance treatment *[see CLINICAL STUDIES (13.2)]*. Patients should be periodically reassessed to determine the need for maintenance treatment.

2.3 Adjunctive Treatment of Major Depressive Disorder

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

2.4 Irritability Associated with Autistic Disorder

Paediatric Patients (6 to 17 years)

The recommended dosage range for the treatment of paediatric 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 (13.4)]*. Patients should be periodically reassessed to determine the continued need for maintenance treatment.

2.5 Tourette's Disorder

Paediatric Patients (6 to 18 years)

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

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

For patients weighing 50 kg or more, dosing should be initiated at 2 mg/day for 2 days, and then increased to 5 mg/day for 5 days, with a target dose of 10 mg/day on day 8. The dose can be increased up to 20 mg/day for patients who do not achieve optimal control of tics. Dosage adjustments should occur gradually in increments of 5 mg/day at intervals of no less than 1 week *[see CLINICAL STUDIES (13.5)]*.

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 co-administered drug is withdrawn from the combination therapy, ABILIFY dosage should then be adjusted to its original level. When the co-administered CYP3A4 inducer is withdrawn, ABILIFY dosage should be reduced to the original level over 1 to 2 weeks. Patients who may be receiving a combination of strong, moderate, and weak inhibitors of CYP3A4 and CYP2D6 (e.g., a strong CYP3A4 inhibitor and a moderate CYP2D6 inhibitor or a moderate CYP3A4 inhibitor with a moderate CYP2D6 inhibitor), the dosing may be reduced to one-quarter (25%) of the usual dose initially and then adjusted to achieve a favourable clinical response.

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

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

When adjunctive ABILIFY is administered to patients with major depressive disorder, ABILIFY should be administered without dosage adjustment as specified in *DOSAGE AND ADMINISTRATION (2.3)*.

2.7 Dosing of Oral Solution

The oral solution can be substituted for tablets on an 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 (11.3)]*

3. CONTRAINDICATIONS

ABILIFY is contraindicated in patients with a history of a hypersensitivity reaction to aripiprazole. Reactions have ranged from pruritus/urticaria to anaphylaxis.

4. WARNINGS AND PRECAUTIONS

4.1 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 to 99 years), the adverse reactions that were reported at an incidence of ≥ 3% and ABILIFY incidence at least twice that for placebo were lethargy [placebo 2%, ABILIFY 5%], somnolence (including sedation) [placebo 3%, ABILIFY 8%], and incontinence (primarily, urinary incontinence) [placebo 1%, ABILIFY 5%], excessive salivation [placebo 0%, ABILIFY 4%], and light-headedness [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 also BOXED WARNING].*

4.2 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 and WARNINGS AND PRECAUTIONS (4.1)]*

4.3 Suicidal Thoughts and Behaviours in Children, Adolescents, and Young Adults

Patients with major depressive disorder (MDD), both adult and paediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behaviour (suicidality) or unusual changes in behaviour, 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 behaviour (suicidality) in children, adolescents, and young adults (ages 18 - 24 years) 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 years; there was a reduction with antidepressants compared to placebo in adults aged 65 years 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 2.

Table 2:

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

No suicides occurred in any of the paediatric 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 behaviour, 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 paediatric patients being treated with antidepressants for MDD as well as for other indications, both psychiatric and non-psychiatric. 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 non-psychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behaviour, 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 paediatric population.

4.4 Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including 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, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and

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

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

4.5 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.

Tardive dyskinesia 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.

4.6 Extrapyramidal symptoms (EPS)

In paediatric clinical trials of aripiprazole, akathisia and Parkinsonism were observed. If signs and symptoms of other EPS appear in a patient taking aripiprazole, dose reduction and close clinical monitoring should be considered.

4.7 Venous Thromboembolism

Cases of venous thromboembolism (VTE) have been reported with antipsychotic drugs. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with ABILIFY and preventive measures undertaken.

4.8 Metabolic Changes

Atypical antipsychotic drugs have been associated with metabolic changes that include hyperglycaemia/diabetes mellitus, dyslipidaemia, 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.

Hyperglycaemia/Diabetes Mellitus

Hyperglycaemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. There have been reports of hyperglycaemia in patients treated with ABILIFY. 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 hyperglycaemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycaemia-related adverse reactions in patients treated with the atypical antipsychotics. Because ABILIFY was not marketed at the time these studies were performed, it is not known if ABILIFY is associated with this increased risk. Precise risk estimates for hyperglycaemia-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 hyperglycaemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycaemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycaemia 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 3 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 3: 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 was slightly lower than in placebo-treated patients. Table 4 shows the proportion of adult patients with changes in fasting glucose levels from three placebo-controlled, adjunctive trials in patients with major depressive disorder.

Table 4: Changes in Fasting Glucose Measurements From Placebo-Controlled Adjunctive Trials in Adult Patients with Major Depressive Disorder

		Treatment Arm	n/N	%
Fasting Glucose	≥ 126 mg/dL	ABILIFY	8/358	2.2
		Placebo	10/362	2.8

Paediatric Patients & Adolescents

In an analysis of two placebo-controlled trials in adolescents with schizophrenia (13 to 17 years) and paediatric 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 paediatric and adolescent patients with irritability

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

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

Table 5 shows the proportion of patients with changes in fasting glucose levels from the pooled adolescent schizophrenia and paediatric bipolar patients (median exposure of 42 to 43 days), from two placebo-controlled trials in paediatric patients (6 to 17 years) with irritability associated with autistic disorder (median exposure of 56 days), and from the two placebo-controlled trials in paediatric patients (6 to 18 years) with Tourette's Disorder (median exposure 57 days).

Table 5: Changes in Fasting Glucose From Placebo-Controlled Trials in Paediatric and Adolescent Patients

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

At 12 weeks in the pooled adolescent schizophrenia and paediatric 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].

Dyslipidaemia

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/non-fasting total cholesterol, fasting triglycerides, fasting LDLs, and fasting/non-fasting HDLs. Analyses of patients with at least 12 or 24 weeks of exposure were limited by small numbers of patients.

Adults

Table 6 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 6: Changes in Blood Lipid Parameters From Placebo-Controlled Monotherapy Trials in Adults

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

In monotherapy trials, the proportion of patients at 12 weeks and 24 weeks with changes from Normal to High in total cholesterol (fasting/non-fasting), fasting triglycerides, and fasting LDL cholesterol were similar between ABILIFY- and placebo-treated patients: at 12 weeks, Total Cholesterol (fasting/non-fasting), 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/non-fasting), 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 7 shows the incidence of patients with changes in total cholesterol (fasting/non-fasting), fasting triglycerides, fasting LDL cholesterol, and HDL cholesterol from three placebo-controlled adjunctive trials in adult patients with major depressive disorder.

Table 7: Incidence of Blood Lipid Parameters From Placebo-Controlled Adjunctive Trials in Adult Patients with Major Depressive Disorder

	Treatment Arm	n/N	%
Total Cholesterol	ABILIFY	33/277	11.9
Normal to High (< 200 mg/dL to ≥ 240 mg/dL)	Placebo	38/280	13.6
Fasting Triglycerides	ABILIFY	39/295	13.2
Normal to High (< 150 mg/dL to ≥ 200 mg/dL)	Placebo	27/277	9.7
Fasting LDL Cholesterol	ABILIFY	16/298	5.4
Normal to High (< 100 mg/dL to ≥ 160 mg/dL)	Placebo	27/308	8.8
HDL Cholesterol	ABILIFY	13/330	3.9
Normal to Low (≥ 40 mg/dL to < 40 mg/dL)	Placebo	14/320	4.4

Paediatric Patients & Adolescents

Table 8 shows the proportion of adolescents with schizophrenia (13 to 17 years) and paediatric 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 8: Changes in Blood Lipid Parameters from Placebo-Controlled Monotherapy Trials in Paediatric and Adolescent Patients in Schizophrenia and Bipolar Disorder

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

In monotherapy trials of adolescents with schizophrenia and paediatric patients with bipolar disorder, the proportion of patients at 12 weeks and 24 weeks with changes from Normal to High in total cholesterol (fasting/non-fasting), fasting triglycerides, and fasting LDL cholesterol were similar

between ABILIFY-and placebo-treated patients: at 12 weeks, Total Cholesterol (fasting/non-fasting), 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/non-fasting), 0/36 (0%) vs. 0/12 (0%); Fasting Triglycerides, 1/47 (2.1%) vs. 1/10 (10.0%), respectively.

Table 9 shows the proportion of patients with changes in total cholesterol (fasting/non-fasting) and fasting triglycerides (median exposure 56 days) and HDL cholesterol (median exposure 55 to 56 days) from two placebo-controlled trials in paediatric patients (6 to 17 years) with irritability associated with autistic disorder.

Table 9: Changes in Blood Lipid Parameters From Placebo-Controlled Trials in Paediatric Patients with Autistic Disorder

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

Table 10 shows the proportion of patients with changes in total cholesterol (fasting/non-fasting) and fasting triglycerides (median exposure 57 days) and HDL cholesterol (median exposure 57 days) from two placebo-controlled trials in paediatric patients (6 to 18 years) with Tourette's Disorder.

Tablet 10: Changes in Blood Lipid Parameters From Placebo-Controlled Trials in Paediatric Patients with Tourette's Disorder

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

Weight Gain

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

Adults

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

In the trials adding ABILIFY to antidepressants, patients first received 8 weeks of antidepressant treatment followed by 6 weeks of adjunctive ABILIFY or placebo in addition to their ongoing antidepressant treatment. The mean change in body weight in patients receiving adjunctive ABILIFY was + 1.6 kg (N = 456) compared to + 0.6kg (N = 451) in patients receiving adjunctive placebo.

Table 11 shows the percentage of patients with weight gain ≥ 7% of body weight by indication.

Table 11: Percentage of Patients From Placebo-Controlled Trials in Adult Patients with Weight Gain ≥ 7% of Body Weight

	Indication	Treatment arm	N	Patients n (%)
Weight gain ≥ 7% of body weight	Schizophrenia[a]	ABILIFY	852	69 (8.1)
		Placebo	379	12 (3.2)
	Bipolar Mania[b]	ABILIFY	719	16 (2.2)
		Placebo	598	16 (2.7)
	Major Depressive Disorder (Adjunctive Therapy)[c]	ABILIFY	456	24 (5.3)
		Placebo	451	4 (0.9)

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

Paediatric Patients & Adolescents

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

In two short-term, placebo-controlled trials in patients (6 to 17 years) with irritability associated with autistic disorder with median exposure of 56 days, the mean change in body weight in ABILIFY-treated

patients was + 1.6 kg (n = 209) compared to + 0.4 kg (n = 98) in placebo-treated patients.

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

Table 12 shows the percentage of paediatric and adolescent patients with weight gain ≥ 7% of body weight by indication.

Table 12: Percentage of Patients From Placebo-Controlled Monotherapy Trials in Paediatric and Adolescent Patients with Weight Gain ≥ 7% of Body Weight

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

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

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

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

In a 52-week open-label, multicentre study evaluating the safety and tolerability of once-daily oral ABILIFY in children and adolescents with Tourette's Disorder (7 to 17 years), 70% of patients were exposed to aripiprazole for 337 to 364 days and 21.7% (15/69) of patients treated with aripiprazole reported weight increased as a treatment-emergent adverse event.

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

4.9 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%); and of paediatric patients 6 to 18 years of age (n = 732) on oral ABILIFY included orthostatic hypotension (0.5%, 0%), postural dizziness (0.4%, 0 %), and syncope (0.2%, 0%) *[see ADVERSE REACTIONS (5.1)]*.

The incidence of a significant orthostatic change in blood pressure (defined as a decrease in systolic blood pressure ≥ 20 mmHg accompanied by an increase in heart rate ≥ 25 bpm when comparing standing to supine values) for ABILIFY was not meaningfully different from placebo (ABILIFY incidence, placebo incidence): in adult oral ABILIFY-treated patients (4%, 2%) and in paediatric oral ABILIFY-treated patients aged 6 to 18 years (0.4%, 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) *[see DRUG INTERACTIONS (6.1)]*.

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

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

4.11 Seizures/Convulsions

In short-term, placebo-controlled trials, patients with a history of seizures excluded seizures/convulsions occurred in 0.1% (3/2467) of undiagnosed adult patients treated with oral ABILIFY and in 0.1% (1/732) of paediatric patients (6 to 18 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. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

4.12 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 (ABILIFY incidence, placebo incidence): in adult patients (n = 2467) treated with oral ABILIFY (11%, 6%) and in paediatric patients age 6 to 17 years (n = 611) (24%, 6%). Somnolence (including sedation) led to discontinuation in 0.3% (8/2467) of adult patients and 3% (20/732) of paediatric patients (6 to 18 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.

4.13 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).

4.14 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 of tablets consistent with good patient management in order to reduce the risk of overdose.

4.15 Dysphagia

Oesophageal 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 (4.1)]*.

4.16 Pathological Gambling and Other Compulsive Behaviours

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 behaviours. Because patients may not recognize these behaviours 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 behaviours 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.

4.17 Sleep apnoea and related disorders

Sleep apnoea and related disorders have been reported in patients treated with atypical antipsychotic drugs, including aripiprazole, with or without concomitant weight gain or prior history of sleep apnoea.

Aripiprazole should be used with caution in patients who have sleep apnoea or risk factors for developing sleep apnoea, which include: overweight/obesity, males, and concomitant use of central nervous system depressants.

4.18 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. 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 details in other sections of the labelling:

- Increased Mortality in Elderly Patients with Dementia-Related Psychosis *[see BOXED WARNING and WARNINGS AND PRECAUTIONS) (4.1)]*
- Cerebrovascular Adverse Events, Including Stroke *[see WARNINGS AND PRECAUTIONS (4.2)]*
- Suicidal Thoughts and Behaviours in Children, Adolescents, and Young Adults *[see BOXED WARNING and WARNINGS AND PRECAUTIONS (4.3)]*

- Neuroleptic Malignant Syndrome (NMS) *[see WARNINGS AND PRECAUTIONS (4.4)]*
- Tardive Dyskinesia *[see WARNINGS AND PRECAUTIONS (4.5)]*
- Extrapyramidal symptoms [*see WARNINGS AND PRECAUTIONS (4.6)]*
- Venous Thromboembolism *[see WARNINGS AND PRECAUTIONS (4.7)]*
- Metabolic Changes *[see WARNINGS AND PRECAUTIONS (4.8)]*
- Orthostatic Hypotension *[see WARNINGS AND PRECAUTIONS (4.9)]*
- Leukopenia, Neutropenia, and Agranulocytosis *[see WARNINGS AND PRECAUTIONS (4.10)]*
- Seizures/Convulsions *[see WARNINGS AND PRECAUTIONS (4.11)]*
- Potential for Cognitive and Motor Impairment *[see WARNINGS AND PRECAUTIONS (4.12)]*
- Body Temperature Regulation *[see WARNINGS AND PRECAUTIONS (4.13)]*
- Suicide *[see WARNINGS AND PRECAUTIONS (4.14)]*
- Dysphagia *[see WARNINGS AND PRECAUTIONS (4.15)]*
- Pathological Gambling and Other Compulsive Behaviours *[see WARNINGS AND PRECAUTIONS (4.16)]*
- Sleep apnoea and related disorders *[see WARNINGS AND PRECAUTIONS (4.17)]*
- Falls *[see WARNINGS AND PRECAUTIONS (4.18)]*

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 paediatric 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 7,619 patient-years of exposure to oral ABILIFY. A total of 3,390 patients were treated with oral ABILIFY for at least 180 days and 1,933 patients treated with oral ABILIFY had at least 1 year of exposure.

ABILIFY has been evaluated for safety in 1,686 patients (6 to 18 years) who participated in multiple-dose, clinical trials in schizophrenia, bipolar mania, autistic disorder, or Tourette's disorder and who had approximately 1,342 patient-years of exposure to oral ABILIFY. A total of 959 paediatric patients were treated with oral ABILIFY for at least 180 days and 556 paediatric 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 non-comparative 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 events represent the proportion of individuals who experienced at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. There was no attempt to use investigator causality assessments; i.e., all reported events are included.

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

5.1 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 ABILIFY was administered in doses ranging from 2 to 30 mg/day.

Commonly Observed Adverse Reactions

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

Adult Patients with Bipolar Mania

Monotherapy

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

Commonly Observed Adverse Events

Commonly observed adverse reactions associated with the use of ABILIFY in patients with bipolar mania (incidence of 5% or greater and ABILIFY incidence at least twice that for placebo) are shown in Table 13.

Table 13: Commonly Observed Adverse Reactions in Short-Term, Placebo-Controlled Trials in Patients with Bipolar Mania Treated with ABILIFY Monotherapy

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

Less Common Adverse Reactions in Adults

Table 14 enumerates the pooled incidence, rounded to the nearest percent, of adverse reactions that occurred during acute therapy (up to 6 weeks in schizophrenia and up to 3 weeks in bipolar mania), including only those reactions that occurred in 2% or more of patients treated with ABILIFY (doses ≥ 2 mg/day) and for which the incidence in patients treated with ABILIFY was greater than the incidence in patients treated with placebo in the combined dataset.

Table 14: Treatment-Emergent Adverse Reactions in Short-Term, Placebo-Controlled Trials in Adult Patients Treated with ABILIFY

	Percentage of Patients Reporting Reaction[a]	
System Organ Class **Preferred Term**	**ABILIFY (n = 1843)**	**Placebo (n = 1166)**
Eye Disorders		
Blurred Vision	3	1
Gastrointestinal Disorders		
Nausea	15	11
Constipation	11	7
Vomiting	11	6
Dyspepsia	9	7
Dry Mouth	5	4
Toothache	4	3
Abdominal Discomfort	3	2
Stomach Discomfort	3	2
General Disorders and Administration Site Conditions		
Fatigue	6	4
Pain	3	2
Musculoskeletal and Connective Tissue Disorders		

Musculoskeletal Stiffness	4	3
Pain in Extremity	4	2
Myalgia	2	1
Muscle Spasms	2	1
Nervous System Disorders		
Headache	27	23
Dizziness	10	7
Akathisia	10	4
Sedation	7	4
Extrapyramidal Disorder	5	3
Tremor	5	3
Somnolence	5	3
Psychiatric Disorders		
Agitation	19	17
Insomnia	18	13
Anxiety	17	13
Restlessness	5	3
Respiratory, Thoracic, and Mediastinal Disorders		
Pharyngolaryngeal Pain	3	2
Cough	3	2

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

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

Adult Patients with Adjunctive Therapy with Bipolar Mania

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

Adverse Reactions Associated with Discontinuation of Treatment

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

Commonly Observed Adverse Reactions

The commonly observed adverse reactions associated with adjunctive ABILIFY and lithium or valproate in patients with bipolar mania (incidence of 5% or greater and incidence at least twice that for

adjunctive placebo) were: akathisia, insomnia, and extrapyramidal disorder.

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

Table 15 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 15: Adverse Reactions in a Short-Term, Placebo-Controlled Trial of Adjunctive Therapy in Patients with Bipolar Disorder

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

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

Paediatric 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 paediatric 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.

Paediatric Patients 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 paediatric 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 paediatric patients with bipolar mania (incidence of 5% or greater and ABILIFY incidence at least twice that for placebo) are shown in Table 16.

Table 16: Commonly Observed Adverse Reactions in Short-Term, Placebo-Controlled Trials of Paediatric Patients (10 to 17 years) with Bipolar Mania Treated with Oral ABILIFY

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

The frequency and type of adverse reactions in adolescents with Bipolar I Disorder were similar to those in adults except for the following reactions: somnolence, extrapyramidal disorder and fatigue. In the

paediatric population, somnolence and fatigue were observed more frequently in patients with bipolar disorder compared to patients with schizophrenia.

Paediatric 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 paediatric 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 paediatric patients with autistic disorder (incidence of 5% or greater and ABILIFY incidence at least twice that for placebo) are shown in Table 17.

Table 17: Commonly Observed Adverse Reactions in Short-Term, Placebo-Controlled Trials of Paediatric 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

Paediatric 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 paediatric 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 paediatric patients with Tourette's disorder (incidence of 5% or greater and ABILIFY incidence at least twice that for placebo) are shown in Table 18.

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

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

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

Table 19 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 paediatric 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 19: Adverse Reactions in Short-Term, Placebo-Controlled Trials of Paediatric Patients (6 to 18 years) Treated with Oral ABILIFY

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

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

[a] Adverse reactions reported by at least 2% of paediatric 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 three placebo-controlled trials of adjunctive ABILIFY in patients with MDD who had an inadequate response to at least two treatments with antidepressants in the current episode, one of them demonstrated prospectively, in which aripiprazole was administered at doses of 2 mg to 20 mg as adjunctive treatment to continued antidepressant therapy for up to 6 weeks.

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. Akathisia, the most common adverse event leading to discontinuation in the aripiprazole group, led to withdrawal of 1.3% of aripiprazole-treated patients and 0% of patients on placebo.

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, blurred vision, and somnolence.

Less Common Adverse Reactions in Adult Patients with Major Depressive Disorder

Table 20 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 20: Treatment Emergent Adverse Events in Short-Term, Placebo- Controlled Adjunctive Trials of Adult Patients with Major Depressive Disorder (flexible doses of 2 to 20 mg/day)

	Percentage of Patients Reporting Reaction[a]	
System Organ Class	**ABILIFY + ADT***	**Placebo + ADT***
Preferred Term	**(n = 547)**	**(n = 538)**
Eye Disorders		
Blurred Vision	6	2
Gastrointestinal Disorders		
Constipation	5	2
Dyspepsia	2	1
General Disorders and Administration Site Conditions		
Fatigue	9	4
Feeling Jittery	2	1
Irritability	2	1
Infections and Infestations		
Upper Respiratory Tract Infection	6	5
Nasopharyngitis	3	2
Investigations		
Weight Increased	3	2
Metabolism and Nutrition Disorders		
Increased Appetite	3	2
Musculoskeletal and Connective Tissue Disorders		

Arthralgia	4	2
Myalgia	3	1
Nervous System Disorders		
Akathisia	23	4
Somnolence	6	3
Dizziness	4	2
Sedation	4	2
Disturbance in Attention	2	1
Psychiatric Disorders		
Restlessness	12	2
Insomnia	8	3

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

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 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] placebo, 7.1%; 10 mg, 8.5%; 15 mg, 8.7%; 20 mg, 7.5%; 30 mg, 12.6%).

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

Objectively collected data from those trials was collected on the Simpson Angus Rating Scale (for EPS), the Barnes Akathisia Scale (for akathisia) and the Assessments of Involuntary Movement Scales (for dyskinesias). In the schizophrenia trials, the objectively collected data did not show a difference between ABILIFY and placebo, with the exception of the Barnes Akathisia Scale (aripiprazole, 0.08; placebo, -0.05). In the paediatric (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, 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 paediatric (10 to 17 years) patients, the incidence of reported EPS-related events, excluding events related to akathisia, for ABILIFY-treated patients was 26% vs. 5% for placebo and the incidence of akathisia-related events for ABILIFY-treated patients was 10% vs. 2% for placebo.

In the adult bipolar mania trials with monotherapy ABILIFY, the Simpson Angus Rating Scale and the

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

Major Depressive Disorder

In the short-term, placebo-controlled trials in major depressive disorder, the incidence of reported EPS-related events, excluding events related to akathisia, for adjunctive ABILIFY- treated patients was 8% vs. 5% for adjunctive placebo-treated patients; and the incidence of akathisia-related events for adjunctive ABILIFY-treated patients was 23% vs. 4% for adjunctive placebo-treated patients.

In the major depressive disorder trials, the Simpson Angus Rating Scale and the Barnes Akathisia Scale showed a significant difference between adjunctive ABILIFY and adjunctive placebo (ABILIFY, 0.27; placebo, 0.01 and ABILIFY, 0.23; placebo, 0.03). Changes in the Assessments of Involuntary Movement Scales were similar for the adjunctive ABILIFY and adjunctive placebo groups.

Autistic Disorder

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

Tourette's Disorder

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

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

Dystonia

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

Additional Findings Observed in Clinical Trials

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

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

A similar profile was observed in a long-term monotherapy study and a long-term adjunctive study with lithium and valproate in bipolar disorder.

Other Adverse Reactions Observed During the Premarketing Evaluation of ABILIFY

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

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

Adults

Blood and Lymphatic System Disorders:

rare – thrombocytopenia

Cardiac Disorders:

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

Eye Disorders:

infrequent – photophobia; *rare* - diplopia

Gastrointestinal Disorders:

infrequent - gastroesophageal reflux disease

General Disorders and Administration Site Conditions:

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

Hepatobiliary Disorders:

rare - hepatitis, jaundice

Immune System Disorders:

rare- hypersensitivity

Injury, Poisoning, and Procedural Complications:

infrequent– fall; *rare* – heat stroke

Investigations:

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

Metabolism and Nutrition Disorders:

frequent –anorexia; *infrequent* - *rare* - hypokalaemia, hyponatremia, hypoglycaemia

Musculoskeletal and Connective Tissue Disorders:

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

Nervous System Disorders:

infrequent - parkinsonism, memory impairment, cogwheel rigidity, hypokinesia, myoclonus,

bradykinesia; *rare* – akinesia, myoclonus, coordination abnormal, speech disorder, Grand Mal convulsion; *<1/10,000 patients* – choreoathetosis

Psychiatric Disorders:

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

Renal and Urinary Disorders:

rare - urinary retention, nocturia

Reproductive System and Breast Disorders:

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

Respiratory, Thoracic, and Mediastinal Disorders:

infrequent - nasal congestion, dyspnoea

Skin and Subcutaneous Tissue Disorders:

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

Vascular Disorders:

infrequent – hypotension, hypertension

Paediatric Patients

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

Eye Disorders:

infrequent – oculogyric crisis

Gastrointestinal Disorders:

infrequent – tongue dry, tongue spasm

Investigations:

frequent – blood insulin increased

Nervous System Disorders:

infrequent – sleep talking

Renal and Urinary Disorders:

frequent – enuresis

Skin and Subcutaneous Tissue Disorders:

infrequent – hirsutism

5.2 Post-marketing Experience

The following adverse events were reported during the post marketing use of aripiprazole. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure: occurrences of blood glucose fluctuation, allergic reaction (anaphylactic reaction, angioedema, laryngospasm or oropharyngeal spasm), hyper sexuality, pathological gambling, hepatic failure, hiccups, oculogyric crisis, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), restless legs syndrome, blood prolactin decreased and sleep-related eating disorder (SRED).

6. DRUG INTERACTIONS

6.1 Drugs Having Clinically Important Interactions with ABILIFY

Table 21: Clinically Important Drug Interactions with ABILIFY:

Concomitant Drug Name or Drug Class	Clinical Rationale	Clinical Recommendation
Strong CYP3A4 Inhibitors (e.g., itraconazole, clarithromycin) or strong CYP2D6 inhibitors (e.g., quinidine, fluoxetine, paroxetine)	The concomitant use of ABILIFY with strong CYP3A4 or CYP2D6 inhibitors increased the exposure of aripiprazole compared to the use of ABILIFY alone *[see CLINICAL PHARMACOLOGY (11.3)]*	With concomitant use of ABILIFY with a strong CYP3A4 inhibitor or CYP2D6 inhibitor, reduce the ABILIFY dosage *[see DOSAGE AND ADMINISTRATION (2.6)]*.
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 (11.3)]*	With concomitant use of ABILIFY with a strong CYP3A4 inducer, consider increasing the ABILIFY dosage *[see DOSAGE AND ADMINISTRATION (2.6)]*.

Antihypertensive Drugs	Due to its alpha adrenergic antagonism, aripiprazole has the potential to enhance the effect of certain antihypertensive agents.	Monitor blood pressure and adjust dose accordingly *[see WARNINGS AND PRECAUTIONS) (4.9)]*.
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 (4.9)]*	Monitor sedation and blood pressure. Adjust dose accordingly.

6.2 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, and 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 (11.3)]*.

Fluoxetine, Paroxetine, and Sertraline

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

Alcohol

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

7. USE IN SPECIFIC POPULATIONS

7.1 Pregnancy

Pregnancy Category C:

Data

Animal Data

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

Pregnant rats were treated with oral doses of 3, 10, and 30 mg/kg/day (1, 3, and 10 times the maximum recommended human dose [MRHD] on a mg/m^2 basis) of aripiprazole during the period of organogenesis. Gestation was slightly prolonged at 30 mg/kg/day. Treatment at high dose of 30mg/kg/day caused a slight delay in foetal development, (decreased foetal weight), undescended testes, and delayed skeletal ossification (also seen at 10 mg/kg/day). There were no adverse effects on embryo foetal or pup survival. Delivered offspring had decreased bodyweights (10 and 30 mg/kg/day), and increased incidences of hepatodiaphragmatic nodules and diaphragmatic hernia at 30 mg/kg (the other dose groups were not examined for these findings). Postnatally, delayed vaginal opening was seen at 10 and 30 mg/kg/day and impaired reproductive performance (decreased fertility rate, corpora lutea, implants, and live foetuses, and increased post-implantation loss, likely mediated through effects on female offspring) was seen at 30 mg/kg/day. Some maternal toxicity was seen at 30 mg/kg/day; however, there was no evidence to suggest that these developmental effects were secondary to maternal toxicity.

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

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

Risk Summary

Neonates exposed to antipsychotic drugs (including ABILIFY) during the third trimesterof pregnancy are at risk for extrapyramidal and/or withdrawal symptoms. Adequate and well controlled studies have not been conducted in pregnant women. Animal reproduction studies were conducted with aripiprazole in rats and rabbits during organogenesis, and in rats during the pre- and post-natal period. Oral aripiprazole administration during organogenesis in rats and/or rabbits at doses higher than the maximum recommended human dose (MRHD) produced foetal death, decreased foetal weight,

undescended testicles, delayed skeletal ossification, skeletal abnormalities, and diaphragmatic hernia. Oral aripiprazole administration during the pre- and post-natal period in rats at doses higher than the maximum recommended human dose (MRHD) produced prolonged gestation stillbirths, decreased pup weight, and decreased pup survival.

Administer ABILIFY during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Clinical Considerations

Foetal/ Neonate Adverse Reactions

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

7.2 Labour and Delivery

The effect of ABILIFY on labour and delivery in humans is unknown.

7.3 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.

7.4 Paediatric Use

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

The pharmacokinetics of aripiprazole and dehydro-aripiprazole in paediatric patients, 10 to 17 years of age, were similar to those in adults after correcting for the differences in body weight *[see CLINICAL PHARMACOLOGY (11.3)]*.

Schizophrenia

Safety and effectiveness in paediatric patients with schizophrenia were established in a 6-week, placebo-controlled clinical trial in 202 paediatric patients aged 13 to 17 years *[see DOSAGE AND ADMINISTRATION (2.1), ADVERSE REACTIONS (5.1)*, and *CLINICAL STUDIES (13.1)]*. Although maintenance efficacy in paediatric patients has not been systematically evaluated, maintenance efficacy

can be extrapolated from adult data along with comparisons of aripiprazole pharmacokinetic parameters in adult and paediatric patients.

Bipolar I Disorder

Safety and effectiveness in paediatric patients with bipolar mania were evaluated in a 4-week, placebo-controlled clinical trial in 197 paediatric patients aged 10 to 17 years. Younger patients are at increased risk of experiencing adverse events associated with aripiprazole. Therefore, ABILIFY is not recommended for use in patients below 13 years of age *[see DOSAGE AND ADMINISTRATION (2.2), ADVERSE REACTIONS (5.1), and CLINICAL STUDIES (13.2)]*. Although maintenance efficacy in paediatric patients has not been systematically evaluated, maintenance efficacy can be extrapolated from adult data along with comparisons of aripiprazole pharmacokinetic parameters in adult and paediatric patients.

The efficacy of adjunctive ABILIFY with concomitant lithium or valproate in the treatment of manic or mixed episodes in paediatric patients has not been systematically evaluated.

Irritability Associated with Autistic Disorder

Safety and effectiveness in paediatric patients demonstrating irritability associated with autistic disorder were established in two 8-week, placebo-controlled clinical trials in 212 paediatric patients aged 6 to 17 years *[see INDICATIONS AND USAGE (1), DOSAGE AND ADMINISTRATION (2.4), ADVERSE REACTIONS (5.1), and CLINICAL STUDIES (13.4)]*. A maintenance trial was conducted in paediatric patients (6 to 17 years of age) with irritability associated with autistic disorder. The first phase of this trial was an open-label, flexibly dosed (aripiprazole 2 to 15 mg/day) phase in which patients were stabilized (defined as > 25% improvement on the ABC-I subscale, and a CGI-I rating of "much improved" or "very much improved") on ABILIFY for 12 consecutive weeks. Overall, 85 patients were stabilized and entered the second, 16-week, double-blind phase where they were randomized to either continue ABILIFY treatment or switch to placebo. In this trial, the efficacy of ABILIFY for the maintenance treatment of irritability associated with autistic disorder was not established.

Tourette's Disorder

Safety and effectiveness of aripiprazole in paediatric 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 paediatric patients *[see DOSAGE AND ADMINISTRATION (2.5), ADVERSE REACTIONS (5.1), and CLINICAL STUDIES (13.5)]*. Maintenance efficacy in paediatric patients has not been systematically evaluated.

Juvenile Animal Studies

Aripiprazole in juvenile rats caused mortality, CNS clinical signs, impaired memory and learning, and delayed sexual maturation when administered at oral doses of 10, 20, 40 mg/kg/day from weaning (21 days old) through maturity (80 days old). At 40 mg/kg/day, mortality, decreased activity, splayed hind limbs, hunched posture, ataxia, tremors and other CNS signs were observed in both genders. In addition, delayed sexual maturation was observed in males. At all doses and in a dose-dependent manner,

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

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

7.5 Geriatric Use

No dosage adjustment is recommended for elderly patients *[see also BOXED WARNING, WARNINGS AND PRECAUTIONS (4.1) and CLINICAL PHARMACOLOGY (11.3)]*.

Of the 13,543 patients treated with oral ABILIFY in clinical trials, 1,073 (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 years and over to determine whether they respond differently from younger subjects.

ABILIFY is not approved for treatment of patients with psychosis associated with Alzheimer's disease *[see also BOXED WARNING and WARNINGS AND PRECAUTIONS (4.1)]*.

7.6 CYP2D6 Poor Metabolizers

Dosage adjustment is recommended in known CYP2D6 poor metabolizers due to high aripiprazole concentrations. Approximately 8% of Caucasians and 3 to 8% of Black/African Americans cannot metabolize CYP2D6 substrates and are classified as poor metabolizers (PM). 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 (6.1)]*. Similarly, PMs have higher exposure to aripiprazole compared to EMs; hence, PMs should have their initial dose reduced by one-half. Laboratory tests are available to identify CYP2D6 PMs. Aripiprazole

does not inhibit or induce the CYP2D6 pathway *[see DOSAGE AND ADMINISTRATION (2.6) and CLINICAL PHARMACOLOGY (11.3)]*.

7.7 Hepatic and Renal Impairment

No dosage adjustment for ABILIFY is required on the basis of a patient's hepatic function (mild to severe hepatic impairment, Child-Pugh score between 5 and 15), or renal function (mild to severe renal impairment, glomerular filtration rate between 15 and 90 mL/minute) [see *CLINICAL PHARMACOLOGY (11.3)*].

7.8 Other Specific Populations

No dosage adjustment for ABILIFY is required on the basis of a patient's sex, race, or smoking status *[see CLINICAL PHARMACOLOGY (11.3)]*.

8. DRUG ABUSE AND DEPENDENCE

8.1 Controlled Substance

ABILIFY is not a controlled substance.

8.2 Abuse and Dependence

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

9. OVERDOSAGE

MedDRA terminology has been used to classify the adverse reactions.

9.1 Human Experience

In clinical trials and in post marketing experience, adverse reactions of deliberate or accidental over

dosage with ABILIFY have been reported worldwide. These include overdoses with 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 1,260 mg of ABILIFY (42 times the maximum recommended daily dose) by a patient who fully recovered. Deliberate or accidental over dosage was also reported in children (age 12 years and younger) involving ABILIFY ingestions up to 195 mg with no fatalities.

Common adverse reactions (reported in at least 5% of all overdose cases) reported with ABILIFY over dosage (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, hypokalaemia, hypotension, lethargy, loss of consciousness, QRS complex prolonged, QT prolonged, pneumonia aspiration, respiratory arrest, status epilepticus and tachycardia.

9.2 Management of Over Dosage

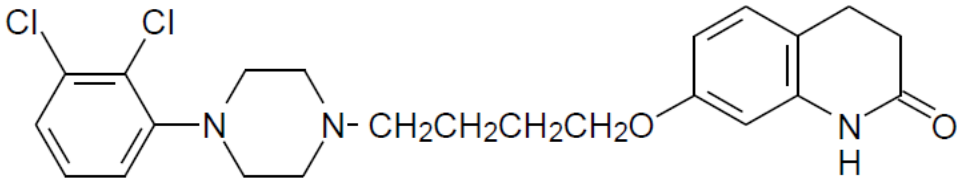
No specific information is available on the treatment of overdose with ABILIFY. An electrocardiogram should be obtained in case of over dosage and, if QTc interval prolongation is present, cardiac monitoring should be instituted. Otherwise, management of overdose should concentrate on supportive therapy,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

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

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

10. DESCRIPTION

ABILIFY® (aripiprazole) is an atypical antipsychotic drug that is available as tablets and oral solution for oral administration. Aripiprazole is 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydrocarbostyril. The empirical formula is $C_{23}H_{27}Cl_2N_3O_2$ and its molecular weight is 448.39. The chemical structure is:



ABILIFY tablets are available in 2-mg, 5-mg, 10-mg, and 15-mg strengths. Inactive ingredients include lactose monohydrate, corn starch, microcrystalline cellulose, hydroxypropyl cellulose, and magnesium stearate. Colorants include Pigment Blend PB-1543 Green, ferric oxide (yellow or red) and FD&C Blue No. 2 Aluminum Lake.

ABILIFY Oral Solution is a clear, colourless to light-yellow solution available in a concentration of 1 mg/mL. The inactive ingredients for this solution include orange oil,ethyl alcohol, disodium edetate, fructose, glycerin, dl-lactic acid, methyl paraben, propylene glycol, propyl paraben, sodium hydroxide, sucrose, and purified water. The oral solution is flavoured with orange flavour.

11. CLINICAL PHARMACOLOGY

ATC Code: N05AX12

11.1 Mechanism of Action

The mechanism of action of aripiprazole, in schizophrenia or bipolar mania, is unknown. However, the efficacy of aripiprazole could be mediated through a combination of partial agonist activity at D_2 and 5-HT_{1A} receptors and antagonist activity at 5-HT_{2A} receptors. Actions at receptors other than D_2, 5-HT_{1A}, and 5-HT_{2A} may explain some of the other clinical effects of aripiprazole (e.g., the orthostatic hypotension observed with aripiprazole may be explained by its antagonist activity at adrenergic $alpha_1$ receptors).

11.2 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.

11.3 Pharmacokinetics

ABILIFY activity is presumably primarily due to the parent drug, aripiprazole, and to a lesser extent, to its major metabolite, dehydro-aripiprazole, which has been shown to have affinities for D_2 receptors similar to the parent drug and represents 40% of the parent drug exposure in plasma. The mean elimination half-lives are about 75 hours and 94 hours for aripiprazole and dehydro-aripiprazole, respectively. Steady-state concentrations are attained within 14 days of dosing for both active moieties. Aripiprazole accumulation is predictable from single-dose pharmacokinetics. At steady state, the pharmacokinetics of aripiprazole is dose-proportional. Elimination of aripiprazole is mainly through hepatic metabolism involving two P450 isozymes, CYP2D6 and CYP3A4. For CYP2D6 poor metabolizers, the mean elimination half-life for aripiprazole is about 146 hours.

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 catalysed by CYP3A4. Aripiprazole is the predominant drug moiety in the systemic circulation. At steady state, dehydro-aripiprazole, the active metabolite, represents about 40% of aripiprazole AUC in plasma.

Following a single oral dose of [^{14}C]-labelled aripiprazole, approximately 25% and 55% of the administered radioactivity was recovered in the urine and faeces, respectively. Less than 1% of

unchanged aripiprazole was excreted in the urine and approximately 18% of the oral dose was recovered unchanged in the faeces.

12. NONCLINICAL TOXICOLOGY

12.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Lifetime carcinogenicity studies were conducted in ICR mice, 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 tumours 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 fibro adenomas 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 tumours. Serum prolactin was not increased in female rats in 4-week and 13-week dietary studies at the dose associated with mammary gland tumours. The relevance for human risk of the findings of prolactin-mediated endocrine tumours in rodents is unknown.

Mutagenesis

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

Impairment of Fertility

Female rats were treated with oral doses of 2, 6, and 20 mg/kg/day (0.6, 2, and 6 times the maximum recommended human dose [MRHD] on a mg/m^2 basis) of aripiprazole from 2 weeks prior to mating through day 7 of gestation. Oestrus 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 foetal 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.

12.2 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.

13. CLINICAL STUDIES

13.1 Schizophrenia

Adults

The efficacy of ABILIFY in the treatment of schizophrenia was evaluated in five short-term (4- 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. The Positive and Negative Syndrome Scale (PANSS) is a multi-item inventory of general psychopathology used to evaluate the effects of drug treatment in schizophrenia. The PANSS positive subscale is a subset of items in the PANSS that rates seven positive symptoms of schizophrenia (delusions, conceptual disorganization, hallucinatory behaviour, excitement, grandiosity, suspiciousness/persecution, and hostility). The PANSS negative subscale is a subset of items in the PANSS that rates seven negative symptoms of schizophrenia (blunted affect, emotional withdrawal, poor rapport, passive apathetic withdrawal, difficulty in abstract thinking, lack of spontaneity/flow of conversation, and stereotyped thinking). The Clinical Global Impression (CGI) assessment reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient.

In a 4-week trial (n = 414) comparing two fixed doses of ABILIFY (15 or 30 mg/day) to placebo, both doses of ABILIFY were superior to placebo in the PANSS total score (Study 1 in Table 22), PANSS positive subscale, and CGI-severity score. In addition, the 15- mg dose was superior to placebo in the PANSS negative subscale.

In a 4-week trial (n = 404) comparing two fixed doses of ABILIFY (20 or 30 mg/day) to placebo, both doses of ABILIFY were superior to placebo in the PANSS total score (Study 2 in Table 22), PANSS positive subscale, PANSS negative subscale, and CGI-severity score.

In a 6-week trial (n = 420) comparing three fixed doses of ABILIFY (10, 15, or 20 mg/day) to placebo, all three doses of ABILIFY were superior to placebo in the PANSS total score (Study 3 in Table 22), PANSS positive subscale, and the PANSS negative subscale.

In a 6-week trial (n = 367) comparing three fixed doses of ABILIFY (2, 5, or 10 mg/day) to placebo, the 10-mg dose of ABILIFY was superior to placebo in the PANSS total score (Study 4 in Table 22), the primary outcome measure of the study. The 2-mg and 5-mg doses did not demonstrate superiority to placebo on the primary outcome measure.

Thus, the efficacy of 10-mg, 15-mg, 20-mg, and 30-mg daily doses was established in two studies for each dose. Among these doses, there was no evidence that the higher dose groups offered any advantage over the lowest dose group of these studies. An examination of population subgroups did not reveal any clear evidence of differential responsiveness on the basis of age, gender, or race.

A longer-term trial enrolled 310 inpatients or outpatients meeting DSM-IV criteria for schizophrenia who were, by history, symptomatically stable on other antipsychotic medications for periods of 3 months or longer. These patients were discontinued from their antipsychotic medications and randomized to ABILIFY 15 mg 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 experienced a significantly longer time to relapse over the subsequent 26 weeks compared to those receiving placebo.

Paediatric Patients

The efficacy of ABILIFY (aripiprazole) in the treatment of schizophrenia in paediatric patients (13 to 17 years of age) was evaluated in one 6-week, placebo-controlled trial of outpatients who met DSM-IV criteria for schizophrenia and had a PANSS score ≥ 70 at baseline. In this trial (n = 302) comparing two fixed doses of ABILIFY (10 or 30 mg/day) to placebo, ABILIFY was titrated starting from 2 mg/day to the target dose in 5 days in the 10 mg/day treatment arm and in 11 days in the 30 mg/day treatment arm. Both doses of ABILIFY were superior to placebo in the PANSS total score (Study 5 in Table 22), 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 paediatric patients has not been systematically evaluated, maintenance efficacy can be extrapolated from adult data along with comparisons of aripiprazole pharmacokinetic parameters in adult and paediatric patients.

Table 22: Schizophrenia Studies

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

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

13.2 Bipolar Disorder

Acute Treatment of Manic and Mixed Episodes

Adults

Monotherapy

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

The primary instrument used for assessing manic symptoms was the Young Mania Rating Scale (Y-MRS), an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology in a range from 0 (no manic features) to 60 (maximum score). A key secondary instrument included the Clinical Global Impression-Bipolar (CGI-BP) Scale.

In the four positive, 3-week, placebo-controlled trials (n = 268; n = 248; n = 480; n = 485) which evaluated ABILIFY in a range of 15 mg to 30 mg, once daily (with a starting dose of 30 mg/day in two studies and 15 mg/day in two studies), ABILIFY was superior to placebo in the reduction of Y-MRS total score (Studies 1 to 4 in Table 23) 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 (YMRS total score ≥ 16 and ≤ 25% improvement on the Y-MRS total score) to lithium or valproate were randomized to receive either ABILIFY (15 mg/day or an increase to 30 mg/day as early as day 7) or placebo as adjunctive therapy with open-label lithium or valproate. In the 6-week, placebo-controlled phase, adjunctive ABILIFY starting at 15 mg/day with concomitant lithium or valproate (in a therapeutic range of 0.6 to 1.0 mEq/L or 50 to 125 µg/mL, respectively) was superior to lithium or valproate with adjunctive placebo in the reduction of the Y-MRS total score (Study 5 in Table 23) and CGI-BP Severity of Illness score (mania). Seventy-one percent of the patients co-administered valproate and 62% of the patients co-administered lithium were on 15 mg/day at 6-week endpoint.

Paediatric Patients

The efficacy of ABILIFY in the treatment of bipolar I disorder in paediatric patients (10 to 17 years of age) was evaluated in one 4-week, placebo-controlled trial (n=296) of outpatients who met DSM-IV criteria for bipolar I disorder manic or mixed episodes with or without psychotic features and had a Y-MRS score ≥ 20 at baseline. This double-blind, placebo-controlled trial compared two fixed doses of ABILIFY (10 or 30 mg/day) to placebo. The ABILIFY dose was started at 2 mg/day, which was titrated to 5 mg/day after 2 days, and to the target dose in 5 days in the 10 mg/day treatment arm, and in 13 days in the 30 mg/day treatment arm. Both doses of ABILIFY were superior to placebo in change from baseline to week 4 on the Y-MRS total score (Study 6 in Table 23).

Table 23: Bipolar Studies

Study	Treatment Group	Primary Efficacy Measure: Y-MRS

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

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

Maintenance Treatment of Bipolar I Disorder

Monotherapy Maintenance Therapy

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

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

Adjunctive Maintenance Therapy

An adjunctive maintenance trial was conducted in adult patients meeting DSMIV criteria for bipolar I disorder with a recent manic or mixed episode. Patients were initiated on open-label lithium (0.6 to 1.0 mEq/L) or valproate (50 to 125 μg/mL) at therapeutic serum levels, and remained on stable doses for 2 weeks. At the end of 2 weeks, patients demonstrating inadequate response (Y-MRS total score ≥ 16 and ≤ 35% improvement on the Y-MRS total score) to lithium or valproate received ABILIFY with a starting dose of 15 mg/day with the option to increase to 30 mg or reduce to 10 mg as early as day 4, as adjunctive therapy with open-label lithium or valproate. Prior to randomization, patients on the combination of single-blind ABILIFY and lithium or valproate were required to maintain stability (Y-MRS and MADRS total scores ≤ 12) for 12 consecutive weeks. Three hundred thirty-seven patients were then randomized in a double-blind fashion, to either the same dose of ABILIFY they were on at the end of the stabilization period or placebo plus lithium or valproate and were then monitored for manic, mixed, or depressive relapse for a maximum of 52 weeks. ABILIFY was superior to placebo on the primary endpoint, time from randomization to relapse to any mood. 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 YMRS 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).

13.3 Adjunctive Treatment of Major Depressive Disorder

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

The primary instrument used for assessing depressive symptoms was the Montgomery-Asberg Depression Rating Scale (MADRS), a 10-item clinician-rated scale used to assess the degree of depressive symptomatology. The key secondary instrument was the Sheehan Disability Scale (SDS), a 3-item self-rated instrument used to assess the impact of depression on three domains of functioning

with each item scored from 0 (not at all) to 10 (extreme).

In the three trials (n = 381, n = 362, n = 349), ABILIFY was superior to placebo in reducing mean MADRS total scores (Studies 1, 2, and 3 in Table 24). In one study, ABILIFY was also superior to placebo in reducing the mean SDS score.

In these 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. All patients who tolerated the initial dose were titrated to at least 10 mg/day. The mean final dose at the end point for the three trials was 10.7, 11.4, and 10.7 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.

The statistical significance of the treatment-by-gender effect in the combined analysis is primarily due to the results of one of 3 studies. Consistent results between males and females were reported in 2 of the 3 studies. The clinical relevance of this apparent treatment-by- gender is unknown.

Clinical trials evaluating ABILIFY in MDD did not include ABILIFY monotherapy treatment arms. It is therefore unknown whether efficacy in adjunct treatment is due to ABILIFY alone or from combined treatment with an ADT.

Table 24: Adjunctive Treatment of Major Depressive Disorder Studies

Study Number	Treatment Group	Primary Efficacy Measure: MADRS		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
Study 1	ABILIFY (5-20 mg/day)* + Antidepressant	25.2(6.2)	-8.49 (0.66)	-2.84 (-4.53 , -1.15)
	Placebo + Antidepressant	27.0 (5.5)	-5.65 (0.64)	--
Study 2	ABILIFY (5-20 mg/day)* + Antidepressant	26.0 (6.0)	-8.78 (0.63)	-3.01 (-4.66 , -1.37)
	Placebo + Antidepressant	26.0 (6.5)	-5.77 (0.67)	--
Study 3	ABILIFY (5-20mg/day) + Antidepressant	26. 22 (6.9)	-10.12 (0.74)	-3.73 (-5.44, -2.02)
	Placebo + Antidepressant	26.72 (6.9)	-6.39 (0.74)	

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.

13.4 Irritability Associated with Autistic Disorder

Paediatric 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 paediatric patients (6 to 17 years of age) who met the DSM-IV criteria for autistic disorder and demonstrated behaviours such as tantrums, aggression, self-injurious behaviour, or a combination of these problems. These patients had clinically significant behavioural problems that were at least moderate in severity, as defined by a CGI-Severity score ≥ 4 and an Irritability Subscale score ≥ 18 on the Aberrant Behaviour Checklist (ABC). Over 75% of these subjects were under 13 years of age.

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

The results of these trials are as follows:

In one of the 8-week, placebo-controlled trials, children and adolescents with autistic disorder (n = 98), aged 6 to 17 years, received daily doses of placebo or ABILIFY 2 to 15 mg/day. ABILIFY, starting at 2 mg/day with increases allowed up to 15 mg/day based on clinical response, significantly improved scores on the ABC-I subscale and on the CGI-I scale compared with placebo. The mean daily dose of ABILIFY at the end of 8week treatment was 8.6 mg/day (Study 1 in Table 25).

In the other 8-week, placebo-controlled trial in children and adolescents with autistic disorder (n = 218), aged 6 to 17 years, three fixed doses of ABILIFY (5 mg/day, 10 mg/day, or 15 mg/day) were compared to placebo. ABILIFY dosing started at 2 mg/day and was increased to 5 mg/day after one week. After a second week, it was increased to 10 mg/day for patients in the 10 and 15 mg dose arms, and after a third week, it was increased to 15 mg/day in the 15 mg/day treatment arm (Study 2 in Table 25). All three doses of ABILIFY significantly improved scores on the ABC-I subscale compared with placebo.

Table 25: Irritability Associated with Autistic Disorder Studies (Paediatric)

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

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval.

[a] Difference (drug minus placebo) in least-squares mean change from baseline.

* Doses statistically significantly superior to placebo.

In a study designed to assess safety and efficacy of Aripiprazole in the long-term maintenance treatment of paediatric patients (6 to 17 years of age) with irritability associated with autistic disorder, the efficacy of ABILIFY for the maintenance treatment of irritability associated with autistic disorder was not established.

This study was a multicentre, double-blind, randomized, placebo-controlled study with 2 parallel treatment groups designed to assess the safety and efficacy of aripiprazole in the long-term maintenance treatment of paediatric subjects with irritability associated with autistic disorder. The study included 2 phases: Phase 1 (stabilization phase) – 13 to 26 weeks of single-blind aripiprazole treatment and Phase 2 (randomization phase) – 16 weeks of double-blind treatment with aripiprazole or placebo.

The primary objective was to evaluate the efficacy of aripiprazole compared with placebo to prevent relapses in paediatric subjects who maintained a response for 12 weeks of aripiprazole treatment for their symptoms of irritability associated with autistic disorder as measured by the time from randomization to relapse.

This study did not meet its primary end point. The Kaplan-Meier relapse rates at Week 16 were 32% for aripiprazole and 50% for placebo ($p = 0.097$; hazard ratio of 0.57; 95% CI: 0.28, 1.12). The effect size observed was smaller than what was used to power the study.

13.5 Tourette's Disorder

Paediatric 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 paediatric patients (6 to 18 years of age) who met the DSM-IV criteria for Tourette's disorder and had a Total Tic score (TTS) $\geq$ 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.

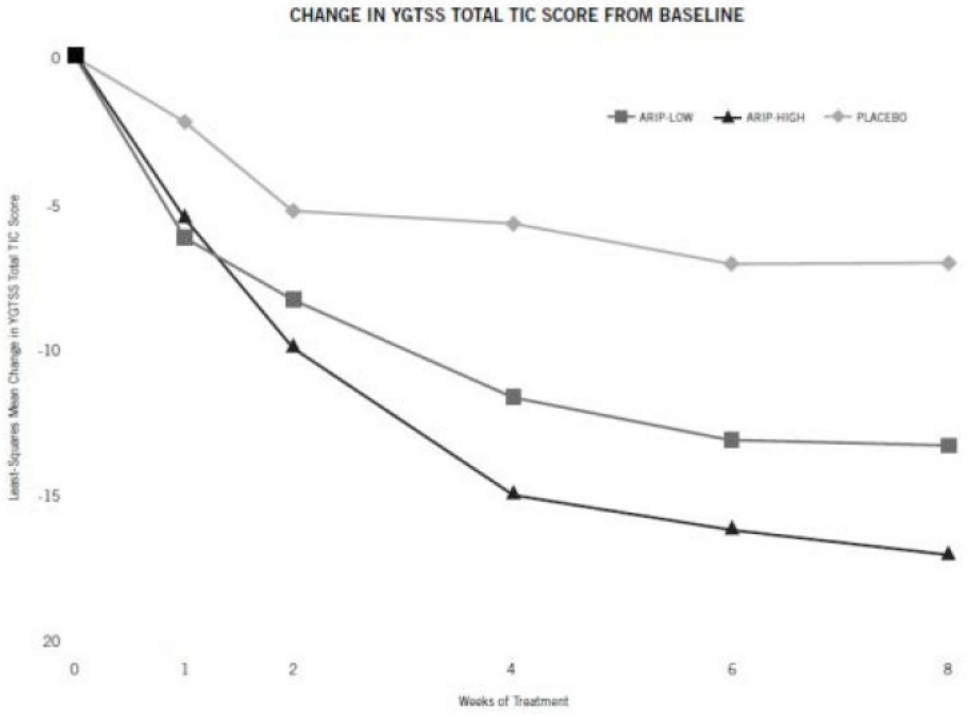
The primary outcome measure in both trials was the change from baseline to endpoint in the TTS of the YGTSS. Ratings for the TTS are made along 5 different dimensions on a scale of 0 to 5 for motor and vocal tics each. Summation of these 10 scores provides a TTS (i.e., 0 to 50).

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 26) 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 1.

Figure 1: 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 26). The mean daily dose of ABILIFY at the end of 10-week treatment was 6.54 mg/day.

Table 26: Tourette's Disorder Studies (Paediatric)

Study Number	Treatment Group	Primary Efficacy Measure: YGTSS TTS		
		Mean Baseline Score (SD)	LS Mean Change from Baseline	Placebo-subtracted Difference[a] (95%

			(SE)	CI)
Study 1	ABILIFY (low dose)*	29.2 (5.63)	-13.4 (1.59)	-6.3 (-10.2, -2.3)
	ABILIFY (high dose)*	31.2 (6.40)	-16.9 (1.61)	-9.9 (-13.8, -5.9)
	Placebo	30.7 (5.95)	-7.1 (1.55)	--
Study 2	ABILIFY (2 to 20 mg/day)*	28.3 (5.51)	-15.0 (1.51)	-5.3 (-9.8, -0.9)
	Placebo	29.5 (5.60)	-9.6 (1.64)	--

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

14. HOW SUPPLIED/STORAGE AND HANDLING

14.1 HOW SUPPLIED

ABILIFY (aripiprazole) Tablets have markings on one side and are available in the following strengths listed in Table 27.

Table 27: ABILIFY Tablet Presentations

Tablet Strength	Tablet Colour/Shape	Tablet Markings	Pack Size
2 mg	green modified rectangle	"A-006" and "2"	Alu/Alu Foil Blister of 30
5 mg	blue modified rectangle	"A-007" and "5" and scored on the other side	Alu/Alu Foil Blister of 28
10 mg	pink modified rectangle	"A-008" and "10"	Alu/Alu Foil Blister of 28
15 mg	yellow round	"A-009" and "15"	Alu/Alu Foil Blister of 28

ABILIFY® (aripiprazole) Oral Solution (1 mg/mL) is supplied in 150 ml amber polyethylene terephthalate (PET) bottles with two-piece child-resistant continuous thread, polypropylene (PP) closures.

14.2 STORAGE

Store below 30º C.

15. PATIENT COUNSELING INFORMATION

Discuss the following issues with patients prescribed ABILIFY:

Clinical Worsening of Depression and Suicide Risk

Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behaviour, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to look for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behaviour and indicate a need for very close monitoring and possibly changes in the medication *[see WARNINGS AND PRECAUTIONS (4.3)]*.

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with ABILIFY and should counsel them in its appropriate use.

Interference with Cognitive and Motor Performance

Because ABILIFY may have the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that ABILIFY therapy does not affect them adversely *[see WARNING AND PRECAUTIONS (4.12)]*.

Nursing

Advise patients that breastfeeding is not recommended with ABILIFY treatment because of the potential for serious adverse reactions in a nursing infant *[see USE IN SPECIFIC POPULATION (7.3)]*.

Concomitant Medication

Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions *[see DRUG INTERACTIONS (6)]*.

Alcohol

Patients should be advised to avoid alcohol while taking ABILIFY.

Heat Exposure and Dehydration

Patients should be advised regarding appropriate care in avoiding overheating and dehydration *[see WARNINGS AND PRECAUTIONS (4.13)]*.

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Otsuka Pharmaceutical Co., Ltd.
Tokyo 101-8535 Japan

Jun 2022
Version 9