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

ABILIFY® (aripiprazole) Tablets
ABILIFY DISCMELT® (aripiprazole) Orally Disintegrating Tablets
ABILIFY® (aripiprazole) Oral Solution
ABILIFY® (aripiprazole) Injection

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS AND SUICIDAL THOUGHTS AND BEHAVIORS WITH ANTIDEPRESSANT DRUGS
See full prescribing information for complete boxed warning.

• Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. ABILIFY is not approved for the treatment of patients with dementia-related psychosis. (5.1)
• Increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants. Monitor for worsening and emergence of suicidal thoughts and behaviors. (5.3)

RECENT MAJOR CHANGES
Warnings and Precautions, Pathological Gambling and Other Compulsive Behaviors (5.7)

ABILIFY is an atypical antipsychotic. The oral formulations are indicated for:
• Schizophrenia (14.1)
• Acute Treatment of Manic and Mixed Episodes associated with Bipolar I (14.2)
• Adjunctive Treatment of Major Depressive Disorder (14.3)
• Irritability Associated with Autistic Disorder (14.4)
• Treatment of Tourette’s disorder (14.5)
The injection is indicated for:
• Agitation associated with schizophrenia or bipolar mania (14.6)

DOSE AND ADMINISTRATION

<table>
<thead>
<tr>
<th></th>
<th>Initial Dose</th>
<th>Recommended Dose</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia</td>
<td>10-15 mg/day</td>
<td>10-15 mg/day</td>
<td>30 mg/day</td>
</tr>
<tr>
<td>adolescents</td>
<td>2 mg/day</td>
<td>10 mg/day</td>
<td>30 mg/day</td>
</tr>
<tr>
<td>Bipolar mania</td>
<td>15 mg/day</td>
<td>15 mg/day</td>
<td>30 mg/day</td>
</tr>
<tr>
<td>Adults: monotherapy</td>
<td>10-15 mg/day</td>
<td>15 mg/day</td>
<td>30 mg/day</td>
</tr>
<tr>
<td>Adults: adjunct to lithium or valproate</td>
<td>2 mg/day</td>
<td>10 mg/day</td>
<td>30 mg/day</td>
</tr>
<tr>
<td>Bipolar mania: pediatric patients</td>
<td>2 mg/day</td>
<td>10 mg/day</td>
<td>30 mg/day</td>
</tr>
<tr>
<td>Major Depressive Disorder – Adults adjunct to antipsychotics</td>
<td>2-5 mg/day</td>
<td>5-10 mg/day</td>
<td>15 mg/day</td>
</tr>
<tr>
<td>Irritability associated with autistic disorder</td>
<td>2 mg/day</td>
<td>5-10 mg/day</td>
<td>15 mg/day</td>
</tr>
<tr>
<td>Tourette’s disorder (2.5)</td>
<td>Patients &lt;50 kg</td>
<td>2 mg/day</td>
<td>5 mg/day</td>
</tr>
<tr>
<td>Patients ≥50 kg</td>
<td>2 mg/day</td>
<td>10 mg/day</td>
<td>20 mg/day</td>
</tr>
<tr>
<td>Agitation associated with schizophrenia or bipolar mania (adults, 2.6)</td>
<td>9.75 mg/1.3 mL injected IM</td>
<td>30 mg/day injected IM</td>
<td></td>
</tr>
</tbody>
</table>

• Oral formulations: Administer once daily without regard to meals (2)
• IM injection: Wait at least 2 hours between doses. Maximum daily dose 30 mg (2.5) 
• Known CYP2D6 poor metabolizers: Half of the usual dose (2.7)

DOSE FORMS AND STRENGTHS

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

Known hypersensitivity to ABILIFY (4)

WARNINGS AND PRECAUTIONS
• Cerebrovascular Adverse Reactions in Elderly Patients with Dementia-Related Psychosis: Increased incidence of cerebrovascular adverse reactions (e.g., stroke, transient ischemic attack, including fatalities) (5.2)
• Neuroleptic Malignant Syndrome: Manage with immediate discontinuation and close monitoring (5.4)

COMMONLY REPORTED ADVERSE REACTIONS

Commonly observed adverse reactions (incidence ≥5% and at least twice that for placebo) were:
• Adult patients with schizophrenia: akathisia
• Pediatric patients (13 to 17 years) with schizophrenia: extrapyramidal disorder, somnolence, and tremor
• Adult patients (monotherapy) with bipolar mania: akathisia, sedation, restlessness, tremor, and extrapyramidal disorder
• Adult patients (adjunctive therapy with lithium or valproate) with bipolar mania: akathisia, insomnia, and extrapyramidal disorder
• Pediatric patients (10 to 17 years) with bipolar mania: somnolence, extrapyramidal disorder, fatigue, nausea, akathisia, blurred vision, salivary hypersecretion, and dizziness
• Adult patients with major depressive disorder (adjunctive treatment to antidepressant therapy): akathisia, restlessness, insomnia, constipation, fatigue, and blurred vision
• Pediatric patients (6 to 17 years) with autistic disorder: sedation, fatigue, vomiting, somnolence, tremor, pyrexia, drooling, decreased appetite, salivary hypersecretion, extrapyramidal disorder, and lethargy
• Pediatric patients (6 to 18 years) with Tourette’s disorder: sedation, somnolence, nausea, headache, nasopharyngitis, fatigue, increased appetite
• Adult patients with agitation associated with schizophrenia or bipolar mania: nausea

Discontinue if clinically appropriate (5.5)

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

DRUG INTERACTIONS

Dosage adjustment due to drug interactions (7.1):

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

USE IN SPECIFIC POPULATIONS

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

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 02/2017
ABILIFY® (aripiprazole)

FULL PRESCRIBING INFORMATION

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

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Schizophrenia

The recommended starting and target dose for ABILIFY is 10 or 15 mg/day administered on a once-a-day schedule without regard to meals. ABILIFY has been systematically evaluated and shown to be effective in a dose range of 10 to 30 mg/day, when administered as the oral tablet formulation; however, doses higher than 10 or 15 mg/day were not more effective than 10 or 15 mg/day. Dosage increases should generally not be made before 2 weeks, the time needed to achieve steady-state [see CLINICAL STUDIES (14.1)]. Maintenance Treatment: Maintenance of efficacy in schizophrenia was demonstrated in a trial involving patients with schizophrenia who had been symptomatically stable on other antipsychotic medications for periods of 3 months or longer. These patients were discontinued from those medications and randomized to either ABILIFY 15 mg/day or placebo, and observed for relapse [see CLINICAL STUDIES (14.1)]. Patients should be periodically reassessed to determine the continued need for maintenance treatment.

Adolescents

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

Switching from Other Antipsychotics

There are no systematically collected data to specifically address switching patients with schizophrenia from other antipsychotics to ABILIFY or concerning concomitant administration with other antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some patients with schizophrenia, more gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized.

ABILIFY® Injection is indicated for the treatment of:

- Agitation associated with schizophrenia or bipolar mania [see CLINICAL STUDIES (14.6)]
2.2 Bipolar I Disorder
Acute Treatment of Manic and Mixed Episodes
Adults: The recommended starting dose in adults is 15 mg given once daily as monotherapy and 10 mg to 15 mg given once daily as adjunctive therapy with lithium or valproate. ABILIFY can be given without regard to meals. The recommended target dose of ABILIFY is 15 mg/day, as monotherapy or as adjunctive therapy with lithium or valproate. The dose may be increased to 30 mg/day based on clinical response. The safety of doses above 30 mg/day has not been evaluated in clinical trials. 
Pediatrics: The recommended starting dose in pediatric patients (10 to 17 years) as monotherapy is 2 mg/day, with titration to 5 mg/day after 2 days, and a target dose of 10 mg/day after 2 additional days. Recommended dosing as adjunctive therapy to lithium or valproate is the same. Subsequent dose increases, if needed, should be administered in 5 mg/day increments. ABILIFY can be given without regard to meals [see CLINICAL STUDIES (14.2)].

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

2.4 Irritability Associated with Autistic Disorder
Pediatric Patients (6 to 17 years)
The recommended dosage range for the treatment of pediatric patients with irritability associated with autistic disorder is 5 to 15 mg/day.

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

2.5 Tourette’s Disorder
Pediatric Patients (6 to 18 years)
The recommended dosage range for Tourette’s Disorder is 5 to 20 mg/day.

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

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

2.6 Agitation Associated with Schizophrenia or Bipolar Mania
(Intramuscular Injection)
Adults
The recommended dose in these patients is 9.75 mg. The recommended dosage range is 5.25 to 15 mg. No additional benefit was demonstrated for 15 mg compared to 9.75 mg. A lower dose of 5.25 mg may be considered when clinical factors warrant. If agitation warranting a second dose persists following the initial dose, cumulative doses up to a total of 30 mg/day may be given. However, the efficacy of repeated doses of ABILIFY injection in agitated patients has not been systematically evaluated in controlled clinical trials. The safety of total daily doses greater than 30 mg or injections given more frequently than every 2 hours have not been adequately evaluated in clinical trials [see CLINICAL STUDIES (14.6)].

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

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

Table 1: ABILIFY Injection Dosing Recommendations

<table>
<thead>
<tr>
<th>Single-Dose</th>
<th>Required Volume of Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.25 mg</td>
<td>0.7 mL</td>
</tr>
<tr>
<td>9.75 mg</td>
<td>1.3 mL</td>
</tr>
<tr>
<td>15 mg</td>
<td>2 mL</td>
</tr>
</tbody>
</table>

ABILIFY Injection is intended for intramuscular use only. Do not administer intravenously or subcutaneously. Inject slowly, deep into the muscle mass. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

2.7 Dosage Adjustments for Cytochrome P450 Considerations
Dosage adjustments are recommended in patients who are known CYP2D6 poor metabolizers and in patients taking concomitant CYP3A4 inhibitors or CYP2D6 inhibitors or strong CYP3A4 inducers (see Table 2). When the coadministered drug is withdrawn from the combination therapy, ABILIFY dosage should then be adjusted to its original level. When the coadministered CYP3A4 inducer is withdrawn, ABILIFY dosage should be reduced to the original level over 1 to 2 weeks. Patients who may be receiving a combination of strong, moderate, and weak inhibitors of CYP3A4 and CYP2D6 (e.g., a strong CYP3A4 inhibitor and a moderate CYP2D6 inhibitor or a moderate CYP3A4 inhibitor with a moderate CYP2D6 inhibitor), the dosing may be reduced to one-quarter (25%) of the usual dose initially and then adjusted to achieve a favorable clinical response.

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

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

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

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

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

3 DOSAGE FORMS AND STRENGTHS

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

Table 3: ABILIFY Tablet Presentations

<table>
<thead>
<tr>
<th>Tablet Strength</th>
<th>Tablet Color/Shape</th>
<th>Tablet Markings</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 mg</td>
<td>green/modified rectangle</td>
<td>“A-006” and “2”</td>
</tr>
<tr>
<td>5 mg</td>
<td>blue/modified rectangle</td>
<td>“A-007” and “2”</td>
</tr>
<tr>
<td>10 mg</td>
<td>pink/modified rectangle</td>
<td>“A-008” and “10”</td>
</tr>
<tr>
<td>15 mg</td>
<td>yellow/round</td>
<td>“A-009” and “15”</td>
</tr>
<tr>
<td>20 mg</td>
<td>white/round</td>
<td>“A-010” and “20”</td>
</tr>
<tr>
<td>30 mg</td>
<td>pink/round</td>
<td>“A-011” and “30”</td>
</tr>
</tbody>
</table>

ABILIFY DISCMELT™ (aripiprazole) Orally Disintegrating Tablets are available as described in Table 4.

Table 4: ABILIFY DISCMELT Orally Disintegrating Tablet Presentations

<table>
<thead>
<tr>
<th>Tablet Strength</th>
<th>Tablet Color/Shape</th>
<th>Tablet Markings</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mg</td>
<td>pink (with scattered specks) round</td>
<td>“A” and “640” and “10”</td>
</tr>
<tr>
<td>15 mg</td>
<td>yellow (with scattered specks) round</td>
<td>“A” and “641” and “15”</td>
</tr>
</tbody>
</table>

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

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

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

5 WARNINGS AND PRECAUTIONS
5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis
Increased Mortality
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. ABILIFY (aripiprazole) is not approved for the treatment of patients with dementia-related psychosis [see BOXED WARNING].
Safety Experience in Elderly Patients with Psychosis Associated with Alzheimer’s Disease

In three, 10-week, placebo-controlled studies of ABILIFY in elderly patients with psychosis associated with Alzheimer’s disease (n=936; mean age: 82.4 years; range: 56-98 years), the adverse reactions that were not reported at an incidence of ≥5% and ABILIFY incidence at least twice that for placebo were lethargy [placebo 2%, ABILIFY 5%], somnolence (including sedation) [placebo 3%, ABILIFY 8%], and incontinence (primarily, urinary incontinence) [placebo 1%, ABILIFY 5%], excessive salivation [placebo 0%, ABILIFY 4%], and lightheadedness [placebo 1%, ABILIFY 4%].

The safety and efficacy of ABILIFY in the treatment of patients with psychosis associated with dementia have not been reported if the prescriber elects to treat these patients with ABILIFY, assess for the emergence of difficulty swallowing or excessive somnolence, which could predispose to accidental injury or aspiration [see BOXED WARNING].

5.2 Cerebrovascular Adverse Events, Including Stroke

In placebo-controlled clinical studies (two flexible dose and one fixed dose study) of dementia-related psychosis, there was an increased incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack), including fatalities, in ABILIFY-treated patients (mean age: 84 years; range: 78-88 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 BOXED WARNING].

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

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist after treatment discontinuation. Therefore, although it 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 placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with MDD and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older. The pooled analyses of placebo-controlled trials in children and adolescents with MDD, Obsessive Compulsive Disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 5.

Table 5:

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18</td>
<td>Increases Compared to Placebo</td>
</tr>
<tr>
<td>14 additional cases</td>
<td>5 additional cases</td>
</tr>
<tr>
<td>25-64</td>
<td>6 fewer cases</td>
</tr>
<tr>
<td>&gt;65</td>
<td>1 fewer case</td>
</tr>
</tbody>
</table>

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide. It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

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

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

5.4 Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) may occur with administration of antipsychotic drugs, including ABILIFY. 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 other causes that could be responsible for the symptoms and signs. 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 diagnosis of NMS may be complicated. In arriving at a diagnosis, it is important to exclude other causes that could be responsible for the symptoms and signs. 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 management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapeutic treatment; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

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

5.5 Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop with treatment 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 be dose-related. The term tardive dyskinesia is used to describe a syndrome in antipsychotic-treated patients characterized by the development of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

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

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

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

5.6 Metabolic Changes

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

Hyperglycemia, in some cases extreme and associated with ketoadosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. There have been reports of hyperglycemia in patients treated with ABILIFY (see ADVERSE REACTIONS (6.1, 6.2)). Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of hyperglycemia-related adverse reactions in patients treated with the atypical antipsychotics. Because ABILIFY was not marketed at the time these studies were performed, it is not known if ABILIFY is associated with this increased risk. Precise risk estimates for hyperglycemia-related adverse reactions in patients treated with atypical antipsychotics are not available.

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

Adults

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

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

<table>
<thead>
<tr>
<th>Category Change (at least once) from Baseline</th>
<th>Treatment Arm</th>
<th>n/N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal to High (&lt;100 mg/dL to ≥126 mg/dL)</td>
<td>ABILIFY</td>
<td>31/822</td>
<td>3.8</td>
</tr>
<tr>
<td>Borderline to High (&lt;100 mg/dL and &lt;126 mg/dL to ≥126 mg/dL)</td>
<td>Placebo</td>
<td>22/605</td>
<td>3.6</td>
</tr>
</tbody>
</table>

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 (+4.7 mg/dL; median exposure 42 days; N=241) was not significantly different than in placebo-treated patients (+0.8 mg/dL; median exposure 42 days; N=246). Table 7 shows the proportion of adult patients with changes in fasting glucose levels from two placebo-controlled, adjunctive trials (median exposure 42 days) in patients with major depressive disorder.

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

<table>
<thead>
<tr>
<th>Category Change (at least once) from Baseline</th>
<th>Treatment Arm</th>
<th>n/N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal to High (&lt;100 mg/dL to ≥126 mg/dL)</td>
<td>ABILIFY</td>
<td>2/201</td>
<td>1.0</td>
</tr>
<tr>
<td>Borderline to High (&lt;100 mg/dL and &lt;126 mg/dL to ≥126 mg/dL)</td>
<td>Placebo</td>
<td>2/204</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Pediatric Patients and Adolescents

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

In an analysis of two placebo-controlled trials in pediatric and adolescent patients with Tourette’s disorder (6 to 18 years) with median exposure of 56 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).

In monotherapy trials in adults, the proportion of patients at 12 weeks and 24 weeks with changes from Normal to High in total cholesterol (fasting/nonfasting), fasting triglycerides, and fasting LDL cholesterol were similar between ABILIFY- and placebo-treated patients. At 12 weeks, Total Cholesterol (fasting/nonfasting), 1/71 (1.4%) vs. 3/74 (4.1%); Fasting Triglycerides, 6/62 (12.9%) vs. 5/37 (13.5%); Fasting LDL Cholesterol, 0/34 (0%) vs. 1/25 (4.0%), respectively; and at 24 weeks, Total Cholesterol (fasting/nonfasting), 1/42 (2.4%) vs. 3/37 (8.1%); Fasting Triglycerides, 5/34 (14.7%) vs. 5/20 (25%); Fasting LDL Cholesterol, 0/22 (0%) vs. 1/18 (5.6%), respectively.

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

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

<table>
<thead>
<tr>
<th>Category Change (at least once) from Baseline</th>
<th>Treatment Arm</th>
<th>n/N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting Glucose Normal to High (&lt;100 mg/dL to ≥126 mg/dL)</td>
<td>ABILIFY</td>
<td>2/236</td>
<td>0.8</td>
</tr>
<tr>
<td>Irritability Associated with Autistic Disorder</td>
<td>Placebo</td>
<td>2/110</td>
<td>1.8</td>
</tr>
<tr>
<td>Tourette’s Disorder</td>
<td>ABILIFY</td>
<td>0/73</td>
<td>0</td>
</tr>
<tr>
<td>Placebo</td>
<td>0/32</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Tourette’s Disorder</td>
<td>ABILIFY</td>
<td>3/88</td>
<td>3.4</td>
</tr>
<tr>
<td>Placebo</td>
<td>1/58</td>
<td>1.7</td>
<td></td>
</tr>
</tbody>
</table>

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

Dyslipidemia

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

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

Adults

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

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

<table>
<thead>
<tr>
<th>Total Cholesterol Normal to High (&lt;200 mg/dL to ≥240 mg/dL)</th>
<th>Treatment Arm</th>
<th>n/N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABILIFY</td>
<td>34/1357</td>
<td>2.5</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>27/973</td>
<td>2.8</td>
<td></td>
</tr>
<tr>
<td>Fasting Triglycerides Normal to High (&lt;150 mg/dL to ≥200 mg/dL)</td>
<td>ABILIFY</td>
<td>40/539</td>
<td>7.4</td>
</tr>
<tr>
<td>Placebo</td>
<td>30/431</td>
<td>7.0</td>
<td></td>
</tr>
<tr>
<td>Fasting LDL Cholesterol Normal to Low (&lt;160 mg/dL to ≥150 mg/dL)</td>
<td>ABILIFY</td>
<td>2/332</td>
<td>0.6</td>
</tr>
<tr>
<td>Placebo</td>
<td>2/288</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>HDL Cholesterol Normal to Low (&lt;40 mg/dL to &lt;40 mg/dL)</td>
<td>ABILIFY</td>
<td>121/1066</td>
<td>11.4</td>
</tr>
<tr>
<td>Placebo</td>
<td>99/794</td>
<td>12.5</td>
<td></td>
</tr>
</tbody>
</table>

In monotherapy trials in adults, the proportion of patients at 12 weeks and 24 weeks with changes from Normal to High in total cholesterol (fasting/nonfasting), fasting triglycerides, and fasting LDL cholesterol were similar between ABILIFY- and placebo-treated patients. At 12 weeks, Total Cholesterol (fasting/nonfasting), 1/71 (1.4%) vs. 3/74 (4.1%); Fasting Triglycerides, 6/62 (12.9%) vs. 5/37 (13.5%); Fasting LDL Cholesterol, 0/34 (0%) vs. 1/25 (4.0%), respectively; and at 24 weeks, Total Cholesterol (fasting/nonfasting), 1/42 (2.4%) vs. 3/37 (8.1%); Fasting Triglycerides, 5/34 (14.7%) vs. 5/20 (25%); Fasting LDL Cholesterol, 0/22 (0%) vs. 1/18 (5.6%), respectively.
ABILIFY® (aripiprazole)

18 years) with Tourette's Disorder.

from two placebo-controlled trials in pediatric patients (6 to

Table 13 shows the proportion of patients with changes in total cholesterol (fasting/nonfasting) and fasting triglycerides (median exposure 57 days) and HDL cholesterol (pooled from two placebo-controlled trials; median exposure 42 to 44 days).

Pediatric Patients and Adolescents

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

<table>
<thead>
<tr>
<th>Indication</th>
<th>Treatment Arm n/N %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia*</td>
<td>ABILIFY 852 69 (8.1)</td>
</tr>
<tr>
<td>Bipolar Mania*</td>
<td>Placebo 379 12 (3.2)</td>
</tr>
<tr>
<td>Major Depressive Disorder (Adjunctive Therapy)*</td>
<td>ABILIFY 347 18 (5.2)</td>
</tr>
</tbody>
</table>

In monotherapy trials of adolescents with schizophrenia and pediatric patients with bipolar disorder, the proportion of patients at 12 weeks and 24 weeks with changes from Normal to High in total cholesterol (fasting/nonfasting), fasting triglycerides, and fasting LDL cholesterol were similar between ABILIFY- and placebo-treated patients: at 12 weeks, Total Cholesterol (fasting/nonfasting), 0/57 (0%) vs. 0/15 (0%); Fasting Triglycerides, 2/72 (2.2%) vs. 1/14 (7.1%), respectively; and at 24 weeks, Total Cholesterol (fasting/nonfasting), 0/36 (0%) vs. 0/12 (0%); Fasting Triglycerides, 1/47 (2.1%) vs. 1/10 (10%), respectively.

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

Weight Gain

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

Adults

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

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

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

Pediciatric Patients and Adolescents

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

In two short-term, placebo-controlled trials in patients (6 to 17 years) with irritability associated with autistic disorder with median exposure of 56 days, the mean change in body weight in ABILIFY-treated patients was +1.6 kg (n=105) compared to +0.4 kg (n=66) in placebo-treated patients.

Table 15 shows the percentage of pediatric and adolescent patients with weight gain ≥7% of body weight by indication.
in an open-label trial that enrolled patients from the two placebo-controlled trials of adolescents with schizophrenia (13 to 17 years) and pediatric patients with bipolar disorder (10 to 17 years), 73.2% of patients (238/325) completed 26 weeks of therapy with ABILIFY. After 26 weeks, 32.8% of patients gained ≥7% of their body weight, not adjusted for normal growth. To adjust for normal growth, z-scores were derived (measured in standard deviations [SD]), which normalize for the natural growth of pediatric patients and adolescents by comparing them to age- and gender-matched population standards. A z-score change <0.5 SD is considered not clinically significant. After 26 weeks, the mean change in z-score was 0.09 SD.

In an open-label trial that enrolled patients from two short-term, placebo-controlled trials, patients (6 to 17 years) with irritability associated with autistic disorder, as well as de novo patients, 60.3% (199/330) completed one year of therapy with ABILIFY. The mean change in weight z-score was 0.26 SDs for patients receiving >9 months of treatment. When treating pediatric patients for any indication, weight gain should be monitored and assessed against that expected for normal growth.

5.7  Pathological Gambling and Other Compulsive Behaviors

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

5.8  Orthostatic Hypotension

ABILIFY may cause orthostatic hypotension, perhaps due to its α1-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): in adult oral ABILIFY-treated patients (9%, 6%), in pediatric patients ages 6 to 17 (n=732) on oral ABILIFY included orthostatic hypotension (0.5%, 0%), postural dizziness (0.5%, 0.3%), atropine (0.5%, 0.4%); of pediatric patients 6 to 18 years of age (n=732) on oral ABILIFY included orthostatic hypotension (0.5%, 0%), postural dizziness (0.4%, 0%), and syncope (0.2%, 0%); and of patients on ABILIFY Injection (n=501) included orthostatic hypotension (0.6%, 0%), postural dizziness (0.2%, 0.5%), and syncope (0.4%, 0%) [see ADVERSE REACTIONS (6.1)].

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

ABILIFY should be used with caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities, or aortic stenosis, or conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications) [see DRUG INTERACTIONS (7.1)]. If parenteral benzodiazepine therapy is deemed necessary in addition to ABILIFY injection treatment, patients should be monitored for excessive sedation and for orthostatic hypotension [see DRUG INTERACTIONS (7.1)].

5.9  Falls

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

5.10  Leukopenia, Neutropenia, and Agranulocytosis

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

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

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

5.11  Seizures/Conversions

In short-term, placebo-controlled trials, patients with a history of seizures excluded. Seizures occurred in 0.1% (3/2467) of undiagnosed adult patients treated with oral ABILIFY, in 0.1% (17/322) of pediatric patients (6 to 18 years), and in 0.2% (1/501) of adult ABILIFY injection-treated patients. As with other antipsychotic drugs, ABILIFY should be used cautiously in patients with a history of seizures or with conditions that lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

5.12  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%), in pediatric patients ages 6 to 17 (n=611) (24%, 6%), and in adult patients (n=501) on ABILIFY Injection (9%, 6%). Somnolence (including sedation) led to discontinuation in 0.3% (8/2467) of adult patients and 3% (20/612) of pediatric patients (6 to 18 years) on oral ABILIFY in short-term, placebo-controlled trials, but did not lead to discontinuation of any adult patients on ABILIFY Injection.

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

5.13  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 are exercising in conditions which may contribute to an elevation in core body temperature, (e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration) [see ADVERSE REACTIONS (6.2)].

5.14  Suicide

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

5.15  Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use, including ABILIFY. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer’s dementia. ABILIFY and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia [see WARNINGS AND PRECAUTIONS (5.12) and ADVERSE REACTIONS (6.2)].

6  ADVERSE REACTIONS

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

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

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

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

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

ABILIFY® (aripiprazole)

ABILIFY® (aripiprazole)
ABILIFY® (aripiprazole)

ABILIFY® has been evaluated for safety in 13,543 adult patients who participated in multiple-dose, clinical trials in schizophrenia, bipolar disorder, major depressive disorder, dementia of the Alzheimer’s type, Parkinson’s disease, and alcoholism, and who had approximately 7619 patient-years of exposure to ORILIX® and 749 patients with exposure to ABILIFY injection. A total of 3390 patients were treated with oral ABILIFY for at least 180 days and 1333 patients treated with oral ABILIFY had at least 1 year of exposure.

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

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

6.1 Clinical Trials Experience

Adult Patients with Schizophrenia

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

Commonly Observed Adverse Reactions

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

Adult Patients with Bipolar Mania

Monotherapy

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

Commonly Observed Adverse Reactions

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

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

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Percentage of Patients Reporting Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ABILIFY (n=917)</td>
</tr>
<tr>
<td>Akathisia</td>
<td>13</td>
</tr>
<tr>
<td>Sedation</td>
<td>6</td>
</tr>
<tr>
<td>Restlessness</td>
<td>6</td>
</tr>
<tr>
<td>Tremor</td>
<td>6</td>
</tr>
<tr>
<td>Extrapyramidal Disorder</td>
<td>5</td>
</tr>
</tbody>
</table>

Less Common Adverse Reactions in Adults

Table 17 enumerates the pooled incidence, rounded to the nearest percent, of adverse reactions that occurred during acute therapy (up to 6 weeks in schizophrenia and up to 3 weeks in bipolar mania), including only those reactions that occurred in 2% or more of patients treated with ABILIFY (doses ≥2 mg/day) and for which the incidence in patients treated with ABILIFY was greater than the incidence in patients treated with placebo in the combined dataset.

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

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Percentage of Patients Reporting Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye Disorders</td>
<td></td>
</tr>
<tr>
<td>Blurred Vision</td>
<td>3</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>15</td>
</tr>
<tr>
<td>Constipation</td>
<td>11</td>
</tr>
<tr>
<td>Vomiting</td>
<td>11</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>9</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>5</td>
</tr>
<tr>
<td>Toothache</td>
<td>4</td>
</tr>
<tr>
<td>Abdominal Discomfort</td>
<td>3</td>
</tr>
<tr>
<td>Stomach Discomfort</td>
<td>3</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>6</td>
</tr>
<tr>
<td>Pain</td>
<td>3</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal Stiffness</td>
<td>4</td>
</tr>
<tr>
<td>Pain in Extremity</td>
<td>4</td>
</tr>
<tr>
<td>Myalgia</td>
<td>2</td>
</tr>
<tr>
<td>Muscle Spasms</td>
<td>2</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>27</td>
</tr>
<tr>
<td>Dizziness</td>
<td>10</td>
</tr>
<tr>
<td>Akathisia</td>
<td>10</td>
</tr>
<tr>
<td>Sedation</td>
<td>7</td>
</tr>
<tr>
<td>Extrapyramidal Disorder</td>
<td>5</td>
</tr>
<tr>
<td>Tremor</td>
<td>5</td>
</tr>
<tr>
<td>Somnolence</td>
<td>5</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td></td>
</tr>
<tr>
<td>Agitation</td>
<td>19</td>
</tr>
<tr>
<td>Insomnia</td>
<td>18</td>
</tr>
<tr>
<td>Anxiety</td>
<td>17</td>
</tr>
<tr>
<td>Restlessness</td>
<td>5</td>
</tr>
<tr>
<td>Respiratory, Thoracic, and Mediastinal Disorders</td>
<td></td>
</tr>
<tr>
<td>Pharyngolaryngeal Pain</td>
<td>3</td>
</tr>
<tr>
<td>Cough</td>
<td>3</td>
</tr>
</tbody>
</table>

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

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

Table 18 enumerates the incidence, rounded to the nearest percent, of adverse reactions that occurred during acute treatment (up to 6 weeks), including only those reactions that occurred in 2% or more of patients treated with adjunctive ABILIFY (doses of 15 or 30 mg/day) and lithium or valproate and for which the incidence in patients treated with this combination was greater than the incidence in patients treated with placebo plus lithium or valproate.
Table 18: Adverse Reactions in a Short-Term, Placebo-Controlled Trial of Adjunctive Therapy in Patients with Bipolar Disorder

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>ABILIFY + Li or Val* (n=253)</th>
<th>Placebo + Li or Val* (n=130)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal Disorders</td>
<td>Nausea</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Salivary Hypersecretion</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Dry Mouth</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td>Nasopharyngitis</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Investigations</td>
<td>Weight Increased</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>Akathisia</td>
<td>19</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Tremor</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Extrapyramidal Disorder</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Sedation</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td>Insomnia</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Anxiety</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Restlessness</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

*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.

Pediatric Patients (13 to 17 years) with Schizophrenia
The following findings are based on one 6-week, placebo-controlled trial in which oral ABILIFY was administered in doses ranging from 2 to 30 mg/day.

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

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

Pediatric Patients (10 to 17 years) with Bipolar Mania
The following findings are based on one 4-week, placebo-controlled trial in which oral ABILIFY was administered in doses of 10 or 30 mg/day.

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

Commonly Observed Adverse Reactions
Commonly observed adverse reactions associated with the use of ABILIFY in pediatric patients with bipolar mania (incidence of 5% or greater and ABILIFY incidence at least twice that for placebo) are shown in Table 19.

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

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>ABILIFY (n=197)</th>
<th>Placebo (n=97)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somnolence</td>
<td>23</td>
<td>3</td>
</tr>
<tr>
<td>Extrapyramidal Disorder</td>
<td>20</td>
<td>3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>Nausea</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>Akathisia</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Blurred Vision</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Salivary Hypersecretion</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>

Pediatric Patients (6 to 17 years) with Tourette’s Disorder
The following findings are based on one 8-week and one 10-week, placebo-controlled trials in which oral ABILIFY was administered in doses of 2 to 20 mg/day.

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

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

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

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>ABILIFY (n=212)</th>
<th>Placebo (n=101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedation</td>
<td>21</td>
<td>4</td>
</tr>
<tr>
<td>Fatigue</td>
<td>17</td>
<td>2</td>
</tr>
<tr>
<td>Vomiting</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>Somnolence</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Tremor</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Drooling</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Decreased Appetite</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Salivary Hypersecretion</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Extrapyramidal Disorder</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Lethargy</td>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>

Pediatric Patients (6 to 18 years) with Tourette’s Disorder
The following findings are based on one 8-week and one 10-week, placebo-controlled trials in which oral ABILIFY was administered in doses of 2 to 20 mg/day.

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

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

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

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>ABILIFY (n=212)</th>
<th>Placebo (n=101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedation</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td>Somnolence</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>Headache</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Increased Appetite</td>
<td>7</td>
<td>1</td>
</tr>
</tbody>
</table>

Less Common Adverse Reactions in Pediatric Patients (6 to 18 years) with Schizophrenia, Bipolar Mania, Autistic Disorder, or Tourette’s Disorder
Table 22 enumerates the pooled incidence, rounded to the nearest percent, of adverse reactions that occurred during acute therapy (up to 6 weeks in schizophrenia, up to 4 weeks in bipolar mania, up to 8 weeks in autistic disorder, and up to 10 weeks in Tourette’s disorder), including only those reactions that occurred in 2% or more of pediatric patients treated with ABILIFY (doses ≥ 2 mg/day) and for which the incidence in patients treated with ABILIFY was greater than the incidence in patients treated with placebo.

Pediatric Patients (6 to 17 years) with Autistic Disorder
The following findings are based on two 8-week, placebo-controlled trials in which oral ABILIFY was administered in doses of 2 to 15 mg/day.

Adverse Reactions Associated with Discontinuation of Treatment
The incidence of discontinuation due to adverse reactions between ABILIFY-treated and placebo-treated pediatric patients (6 to 17 years) was 10% and 8%, respectively.
Table 22: Adverse Reactions in Short-Term, Placebo-Controlled Trials of Pediatric Patients (6 to 18 years) Treated with Oral ABILIFY

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>ABILIFY (n=732)</th>
<th>Placebo (n=370)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye Disorders</td>
<td>Blurred Vision</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Abdominal Discomfort</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Salivary Hypersecretion</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Abdominal Pain Upper</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td>Fatigue</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Pyrexia</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Irritability</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Asthenia</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td>Nasopharyngitis</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Investigations</td>
<td>Weight Increased</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td>Increased Appetite</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Decreased Appetite</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Musculoskeletal and Connective Tissue Disorders</td>
<td>Musculoskeletal Stiffness</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Muscle Rigidity</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>Somnolence</td>
<td>16</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Sedation</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Tremor</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Extrapyramidal Disorder</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Akathisia</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Drooling</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Lethargy</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Dystonia</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Respiratory, Thoracic, and Mediastinal Disorders</td>
<td>Epistaxis</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td>Rash</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

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

Adult Patients Receiving ABILIFY as Adjunctive Treatment of Major Depressive Disorder

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

Adverse Reactions Associated with Discontinuation of Treatment

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

Commonly Observed Adverse Reactions

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

Less Common Adverse Reactions in Adult Patients with Major Depressive Disorder

Table 23 enumerates the pooled incidence, rounded to the nearest percent, of adverse reactions that occurred during acute therapy (up to 6 weeks), including only those adverse reactions that occurred in 2% or more of patients treated with adjunctive ABILIFY (doses ≥2 mg/day) and for which the incidence in patients treated with adjunctive ABILIFY was greater than the incidence in patients treated with adjunctive placebo in the combined dataset.

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

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>ABILIFY+ADT (n=371)</th>
<th>Placebo+ADT (n=306)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye Disorders</td>
<td>Blurred Vision</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>Constipation</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td>Fatigue</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Feeling Jittery</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Infections and Infestations</td>
<td>Upper Respiratory Tract Infection</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Investigations</td>
<td>Weight Increased</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td>Increased Appetite</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Arthralgia</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Myalgia</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>Akathisia</td>
<td>25</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Somnolence</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Tremor</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Sedation</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Disturbance in Attention</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Extrapyramidal Disorder</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td>Restlessness</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Insomnia</td>
<td>8</td>
<td>2</td>
</tr>
</tbody>
</table>

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

* Antidepressant Therapy

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

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

Commonly Observed Adverse Reactions

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

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

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

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

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>Percentage of Patients Reporting Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Disorders</td>
<td>Tachycardia</td>
<td>2 &lt;1</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>Nausea</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>3</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td>Fatigue</td>
<td>2</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>Headache</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>Dizziness</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Somnolence</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Sedation</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Akathisia</td>
<td>2</td>
</tr>
</tbody>
</table>

* Adverse reactions reported by at least 2% of patients treated with ABILIFY injection, except adverse reactions which had an incidence equal to or less than placebo.
Dose-Related Adverse Reactions

Schizophrenia

Dose response relationships for the incidence of treatment-emergent adverse events were evaluated from four trials in adult patients with schizophrenia comparing various fixed doses (2, 5, 10, 15, 20, and 30 mg/day) of oral ABILIFY to placebo. This analysis, stratified by study, indicated that the only adverse reaction to have a possible dose response relationship, and then most prominent only with 30 mg, was somnolence [including sedation]; (incidences were placebo, 7.1%; 10 mg, 8.5%; 15 mg, 8.7%; 20 mg, 7.5%; 30 mg, 12.6%). In the study of pediatric patients (13 to 17 years of age) with schizophrenia, three common adverse reactions appeared to have a possible dose response relationship: extrapyramidal disorder (incidences were placebo, 5.0%; 10 mg, 13.0%; 30 mg, 21.6%); somnolence (incidences were placebo, 6.0%; 10 mg, 11.0%; 30 mg, 21.6%); and tremor (incidences were placebo, 2.0%; 10 mg, 2.0%; 30 mg, 11.8%).

Bipolar Mania

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

Autistic Disorder

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

Tourette’s Disorder

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

Extrapyramidal Symptoms

Schizophrenia

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

Objectively collected data on the Simpson Angus Rating Scale (for EPS), the Barnes Akathisia Scale (for akathisia), and the Assessments of Involuntary Movement Scales (for dyskinesias) were placebo (ABILIFY, 0.08; placebo, –0.05). In the pediatric (13 to 17 years) schizophrenia trial, the objectively collected data did not show a difference between ABILIFY and placebo, with the exception of the Barnes Akathisia Scale (ABILIFY, 0.1; placebo, –0.1).

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

Bipolar Mania

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

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

In the pediatric (10 to 17 years), short-term, bipolar mania trial, the Simpson Angus Rating Scale showed a significant difference between ABILIFY and placebo (ABILIFY, 0.90; placebo, –0.05). Changes in the Barnes Akathisia Scale and the Assessments of Involuntary Movement Scales were similar for the ABILIFY and placebo groups.

Major Depressive Disorder

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

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

Autistic Disorder

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

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

Tourette’s Disorder

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

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

Agitation Associated with Schizophrenia or Bipolar Mania

In the placebo-controlled trials in patients with agitation associated with schizophrenia or bipolar mania, the incidence of reported EPS-related events excluding events related to akathisia for ABILIFY-treated patients was 2% vs. 2% for placebo and the incidence of akathisia-related events for ABILIFY-treated patients was 2% vs. 0% for placebo.

Objectively collected data on the Simpson Angus Rating Scale (for EPS) and the Barnes Akathisia Scale (for akathisia) for all treatment groups did not show a difference between ABILIFY and placebo.

Dystonia

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

Additional Findings Observed in Clinical Trials

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

The adverse reactions reported in a 26-week, double-blind trial comparing oral ABILIFY and placebo in patients with schizophrenia were generally consistent with those reported in the short-term, placebo-controlled trials, except for a higher incidence of tremor (9% (12/135) for ABILIFY vs. 2% (9/315) for placebo). In this study, the majority of the cases of tremor were of mild intensity (8/12 mild and 4/12 moderate), occurred early in therapy (9/12 ≤49 days), and were of limited duration (7/12 ≤10 days). Tremor infrequently led to discontinuation (<1%) of ABILIFY. In addition, in a long-term (52 week), active-controlled study, the incidence of tremor was 5% (40/859) for ABILIFY. A similar profile was observed in a long-term monotherapy study and a long-term adjunctive study with lithium and valproate in bipolar disorder.

Other Adverse Reactions Observed During the Premarketing Evaluation of ABILIFY

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

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

Adults - Oral Administration

Blood and Lymphatic System Disorders:
rare - thrombocytopenia

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

Eye Disorders:
infrequent – photophobia; rare - diplopia

Gastrointestinal Disorders:
infrequent - gastroesophageal reflux disease
Additional adverse reactions observed in the ABILIFY injection population are listed below.

Most adverse reactions observed in the pooled database of 749 adult patients treated with ABILIFY are:

- **Skin and Subcutaneous Tissue Disorders:**
  - hirsutism
- **Renal and Urinary Disorders:**
  - hematuria
- **Nervous System Disorders:**
  - tremor
  - somnolence
  - respiratory distress and feeding disorder

Other reactions observed in the postmarketing surveillance of 1,686 pediatric patients aged 6 to 18 years, as well as in the adult population, are listed below.

- **Eye Disorders:**
  - oculogyric crisis
- **Gastrointestinal Disorders:**
  - tongue dry, tongue spasm
- **Nervous System Disorders:**
  - sleep talking
- **Renal and Urinary Disorders:**
  - enuresis
- **Skin and Subcutaneous Tissue Disorders:**
  - hirsutism

**Adults - Intramuscular Injection**

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

**General Disorders and Administration Site Conditions:**
- frequent - asthenia, infrequent - peripheral edema, chest pain; rare - face edema

**Hepatobiliary Disorders:**
- rare - hepatitis, jaundice

**Imune System Disorders:**
- rare - hypersensitivity

**Injury, Poisoning, and Procedural Complications:**
- infrequent - fall; rare - heat stroke

**Infections:**
- frequent - blood insulin increased

**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 hemoglobin increased

**Metabolism and Nutrition Disorders:**
- frequent - anorexia, rare - hypokalemia, hyponatremia, hypoglycemia

**Musculoskeletal and Connective Tissue Disorders:**
- infrequent - muscular weakness, muscle tightness; rare - rhabdomyolysis, mobility decreased

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

**Psychiatric Disorders:**
- infrequent - aggression, loss of libido, delirium; rare - libido increased, anorgasmia, tic, homicidal ideation, catatonia, sleep walking

**Renal and Urinary Disorders:**
- rare - urinary retention, nocturia

**Reproductive System and Breast Disorders:**
- infrequent - erectile dysfunction; rare - gynaecomastia, menstruation irregular, amenorrhea, breast pain, priapism

**Respiratory, Thoracic, and Mediastinal Disorders:**
- infrequent - nasal congestion, dyspnea

**Skin and Subcutaneous Tissue Disorders:**
- infrequent - rash, hyperhidrosis, pruritus, photosensitivity reaction, alopecia; rare - urticaria

**Vascular Disorders:**
- infrequent - hypotension, hypertension

**Pediatric Patients - Oral Administration**

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

**Eye Disorders**
- infrequent - oculogyric crisis

**Gastrointestinal Disorders**
- infrequent - tongue dry, tongue spasm

**Investigations:**
- frequent - blood insulin increased

**Nervous System Disorders**
- infrequent - sleep talking

**Renal and Urinary Disorders**
- frequent - enuresis

**Skin and Subcutaneous Tissue Disorders**
- infrequent - hirsutism

**Fetal/Neonatal Adverse Reactions**

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Extrapyramidal and/or withdrawal symptoms, including agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder have been reported in neonates who were exposed to antipsychotic drugs (including ABILIFY) during the third trimester of pregnancy. These symptoms have varied in severity. Some neonates recovered within hours or days without specific treatment; others required prolonged hospitalization. Monitor neonates for extrapyramidal and/or withdrawal symptoms.
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/m² basis) of aripiprazole during the period of organogenesis. Gestation was slightly prolonged at 30 mg/kg/day. Treatment at the highest dose of 30 mg/kg/day caused a slight delay in fetal development (decreased fetal weight, undescended testes, and delayed fetal ossification) (also seen at 10 mg/kg/day). There were no adverse effects on embryo/fetal or pup survival. Delivered offspring had decreased body weights (10 and 30 mg/kg/day), and increased incidences of hepaticadipomatous nodules and diaphragmatic hernia at 30 mg/kg (the other dose groups were not examined for these findings). Postnatally, delayed vaginal opening was seen at 10 and 30 mg/kg/day and impaired reproductive performance (decreased fertility rate, corpora lutea, implants, live fetuses, and increased post-implantation loss, likely mediated through effects on female offspring) was seen at 30 mg/kg/day. Some maternal toxicity was seen at 30 mg/kg/day however, there was no evidence to suggest that these developmental effects were secondary to maternal toxicity.

In pregnant rats receiving aripiprazole injection intravenously (3, 9, and 27 mg/kg/day) during the period of organogenesis, decreased fetal weight and delayed fetal ossification were seen at the highest dose where it also caused maternal toxicity. Pregnant rabbits were treated with oral doses of 10, 30, and 100 mg/kg/day (2, 3, and 11 times human exposure at MRHD based on AUC and 6, 19, and 65 times the MRHD based on mg/m²) of aripiprazole during the period of organogenesis. At the high dose of 100 mg/kg/day decreased maternal food consumption, and increased abortions were seen as well as increased fetal mortality, decreased fetal weight (also seen at 30 mg/kg/day), increased incidence of a skeletal abnormality (fused sternebrae) (also seen at 30 mg/kg/day).

In pregnant rabbits receiving aripiprazole injection intravenously (3, 10, and 30 mg/kg/day) during the period of organogenesis, the highest dose, which caused pronounced maternal toxicity, resulted in decreased fetal weight, increased fetal abnormalities (primarily skeletal), and decreased fetal ossification. The fetal no-effect dose was 10 mg/kg/day, which is 5 times the human exposure at the MRHD based on AUC and is 6 times the MRHD based on mg/m².

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

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

8.2 Labor and Delivery

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

Safety and effectiveness in pediatric patients with major depressive disorder or agitation associated with schizophrenia or bipolar mania have not been established. The pharmacoekinetis of aripiprazole and dehydro-aripiprazole in pediatric patients, 10 to 17 years of age, were similar to those in adults after correcting for the differences in body weight [see CLINICAL PHARMACOLOGY (12.3)].

8.5 Geriatric Use

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

Oral Aripiprazole in schizophrenia, bipolar mania, or major depressive disorder did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

Of the 749 patients treated with oral Aripiprazole injection in clinical trials, 99 (13%) were ≥65 years old and 78 (10%) were ≥75 years old. Placebo-controlled studies of oral Aripiprazole in schizophrenic, bipolar mania, or major depressive disorder did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects.

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

8.6 CYP2D6 Poor Metabolizers

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

8.7 Hepatic and Renal Impairment

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

8.8 Other Specific Populations

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

ABILIFY® is not a controlled substance.

9.2 Abuse

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

9.3 Dependence

In physical dependence studies in monkeys, withdrawal symptoms were observed upon abrupt cessation of dosing. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed.

10 OVERDOSE

MedDRA terminology has been used to classify the adverse reactions.

10.1 Human Experience

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

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

10.2 Management of Overdose

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

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

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

11 DESCRIPTION

Aripiprazole is a psychotropic drug that is available as ABILIFY® (aripiprazole) Tablets, ABILIFY DISCMELT® (aripiprazole) Orally Disintegrating Tablets, ABILIFY® (aripiprazole) Oral Solution, and ABILIFY® (aripiprazole) Injection, a solution for intramuscular injection. Aripiprazole is 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl][butoy]-3,4-dihydrocortostyryl. The empirical formula is C23H27Cl2N3O2 and its molecular weight is 448.38. The chemical structure is:

![Chemical Structure of Aripiprazole](https://example.com/chemical_structure.png)

Aripiprazole Tablets are available in 2 mg, 5 mg, 10 mg, 15 mg, 20 mg, and 30 mg strengths. Inactive ingredients include cornstarch, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, and microcrystalline cellulose. Colorants include ferric oxide (yellow or red) and FD&C Blue No. 2 Aluminum Lake.

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

ABILIFY Oral Solution is a clear, colorless to light-yellow solution available in a concentration of 1 mg/mL. The inactive ingredients for this solution include disodium edetate, fructose, gum arabic, dl-lactic acid, methylparaben, propylene glycol, propylparaben, sodium hydroxide, sucrose, and purified water. The oral solution is flavored with natural orange cream and other natural flavors.

ABILIFY® (aripiprazole) ABILIFY® (aripiprazole) Injection is available in single-dose vials as a ready-to-use, 9.75 mg/1.3 mL (7.5 mg/mL) clear, colorless, sterile, aqueous solution for intramuscular use only. Inactive ingredients for this solution include 199.5 mg of sulfobutyl ether p-cyclodextrin (SBECD), 10.4 mg of tartaric acid, qs to pH 4.3 of sodium hydroxide, and qs to 1.33 mL of water for injection.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of aripiprazole in schizophrenia or bipolar mania, is unknown. However, the efficacy of aripiprazole could be mediated through a combination of partial agonist activity at D2 and 5-HT1A receptors and antagonist activity at 5-HT2A receptors. Actions at receptors other than D2, 5-HT1A, and 5-HT2A may explain some of the other clinical effects of aripiprazole (e.g., the orthostatic hypotension observed with aripiprazole may be explained by its antagonist activity at adrenergic alpha1 receptors).

12.2 Pharmacodynamics

Aripiprazole exhibits high affinity for dopamine D2, D3, serotonin 5-HT2A and 5-HT2C receptors (Kd values of 0.34 nM, 0.8 nM, 1.7 nM, and 3.4 nM, respectively), moderate affinity for dopamine D3, serotonin 5-HT2A and 5-HT2C, alpha-adrenergic and histamine H1 receptors (Kd values of 44 nM, 15 nM, 39 nM, 57 nM, and 61 nM, respectively), and moderate affinity for the serotonin reuptake site (Kd = 98 nM). Aripiprazole has no appreciable affinity for cholinergic muscarinic receptors (IC50>1000 nM). [Aripiprazole functions as a partial agonist at the dopamine D3 and the serotonin 5-HT2A receptors as an antagonist at serotonin 5-HT2A receptor.]

12.3 Pharmacokinetics

Aripiprazole 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 D3 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 isoforms, CYP2D6 and CYP3A4. For CYP2D6 poor metabolizers, the mean elimination half-life for aripiprazole is about 146 hours. Pharmacokinetic studies showed that ABILIFY DISCMELT Orally Disintegrating Tablets were bioequivalent to ABILIFY Tablets.

ORAL ADMINISTRATION

Absorption

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

Oral Solution: Aripiprazole is well absorbed when administered orally as the solution. At equivalent doses, the plasma concentrations of aripiprazole from the solution were higher than that from the tablet formulation. In a relative bioavailability study comparing the pharmacokinetics of 30 mg aripiprazole as the oral solution to 30 mg aripiprazole tablets in healthy subjects, the solution to tablet ratios of geometric mean Cmax and AUC values were 122% and 114%, respectively [See DOSAGE AND ADMINISTRATION (2.6)]. The single-dose pharmacokinetics of aripiprazole were linear and dose-proportional between the doses of 5 mg to 30 mg.

Distribution

The steady-state volume of distribution of aripiprazole following intravenous administration is high (404 L or 4.9 L/kg), indicating extensive extravascular distribution. At therapeutic concentrations, aripiprazole and its major metabolite are greater than 99% bound to serum proteins, primarily to albumin. In healthy human volunteers administered 0.5 to 30 mg/day aripiprazole for 14 days, there was dose-dependent D2 receptor occupancy indicating brain penetration of aripiprazole in humans.

Metabolism and Elimination

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

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

Drug Interaction Studies

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

![Graph showing the effects of other drugs on aripiprazole pharmacokinetics](image)

The effects of ABILIFY on the exposures of other drugs are summarized in Figure 3. A population PK analysis in patients with major depressive disorder showed no substantial change in plasma concentrations of fluoxetine (20 or 40 mg/day), paroxetine CR (37.5 or 50 mg/day), or sertraline (100 or 150 mg/day) dosed to steady-state. The steady-state plasma concentrations of fluoxetine and norfluoxetine increased by about 18% and 36%, respectively, and concentrations of paroxetine decreased by about 27%. The steady-state plasma concentrations of sertraline and desmethylsertraline were not substantially changed when these antidepressant therapies were coadministered with aripiprazole.

Figure 2: The effects of other drugs on dehydro-aripiprazole pharmacokinetics
Effect of Other Drugs on Ability

![Graph showing the effects of other drugs on dehydro-aripiprazole pharmacokinetics](image)

INTRAMUSCULAR ADMINISTRATION

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

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Lifetime carcinogenicity studies were conducted in ICR mice, Sprague-Dawley (SD) rats, and F344 rats. Aripiprazole was administered for 2 years in the diet at doses of 1, 3, 10, and 30 mg/kg/day to ICR mice and 1, 3, and 10 mg/kg/day to F344 rats (0.2 to 5 times and 0.3 to 3 times the maximum recommended human dose [MRHD] based on mg/m², respectively). In addition, SD rats were dosed orally for 2 years at 10, 20, and 40 mg/kg/day (3 to 19 times the MRHD based on mg/m²). Aripiprazole did not induce tumors in male mice or male rats. In female mice, the incidences of pituitary gland adenomas and mammary gland adenocarcinomas and adenocantheommas 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/m²). In female rats, the incidence of mammary gland fibroadenomas was increased at a dietary dose of 10 mg/kg/day (0.1 times human exposure at MRHD based on AUC and 3 times the MRHD based on mg/m²), and the incidences of adenocortical carcinomas and combined adenocortical 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/m²).

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

Mutagenesis

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

Impairment of Fertility

Female rats were treated with oral doses of 2, 6, and 20 mg/kg/day (0.6, 2, and 6 times the maximum recommended human dose [MRHD] on a mg/m² basis) of aripiprazole from 9 weeks prior to mating through mating. Estrus cycle irregularities and increased corpora lutea were seen at all doses, but no impairment of fertility was seen. Increased pre-implantation loss was seen at 6 and 20 mg/kg/day and decreased fetal weight was seen at 20 mg/kg/day. Male rats were treated with oral doses of 20, 40, and 60 mg/kg/day (6, 13, and 19 times the MRHD on a mg/m² basis) of aripiprazole from 9 weeks prior to mating through mating. Disturbances in spermatogenesis were seen at 60 mg/kg and prostate atrophy was seen at 40 and 60 mg/kg, but no impairment of fertility was seen.

13.2 Animal Toxicology and/or Pharmacology

Aripiprazole produced retinal degeneration in albino rats in a 26-week chronic toxicity study at a dose of 60 mg/kg and in a 2-year carcinogenicity study at doses of 40 and 60 mg/kg. The 40 and 60 mg/kg/day doses are 1.3 and 19 times the maximum recommended human dose (MRHD) based on mg/m² and 7 to 14 times human exposure at MRHD based on AUC. Evaluation of the retinas of albino mice and of monkeys did not reveal evidence of retinal degeneration. Additional studies to further evaluate the mechanism have not been performed. The relevance of this finding to human risk is unknown.

14 CLINICAL STUDIES

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

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

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

- Three 24-hour trials in agitated adult patients with schizophrenia or mania/mixed episodes of bipolar I disorder [see CLINICAL STUDIES (14.6)]
The efficacy of ABILIFY as monotherapy in the acute treatment of manic episodes was established in a 6-week, placebo-controlled study (n=384) with a 2-week lead-in mood stabilizer monotherapy phase in adult patients who met DSM-IV criteria for bipolar I disorder. This study included patients with manic or mixed episodes and with or without psychotic features.

Patients were initiated on open-label lithium (0.6 to 1.0 mEq/L) or valproate (50 to 125 μg/mL) at therapeutic serum levels, and remained on stable doses for 2 weeks. At the end of 2 weeks, patients demonstrating inadequate response (Y-MRS total score ≥16 and ≤25% improvement on the Y-MRS total score) to lithium or valproate were randomized to receive either ABILIFY (15 mg/day or an increase to 30 mg/day as early as day 7) or placebo as adjunctive therapy with open-label lithium or valproate. In the 6-week, placebo-controlled phase, adjunctive ABILIFY starting at 15 mg/day with concomitant lithium or valproate (in a therapeutic range of 0.6 to 1.0 mEq/L or 50 to 125 μg/mL, respectively) was superior to lithium or valproate with adjunctive placebo in the reduction of the Y-MRS total score (Study 5 in Table 27) and CGI-BP Severity of Illness score (mania). Seventy-one percent of the patients coadministered valproate and 62% of the patients coadministered lithium were on 15 mg/day at 6-week endpoint.

Pediatric Patients

The efficacy of ABILIFY in the treatment of bipolar I disorder in pediatric patients (10 to 17 years of age) was evaluated in one 4-week, placebo-controlled trial (n=296) of outpatients who met DSM-IV criteria for bipolar I disorder manic or mixed episodes with or without psychotic features and had a Y-MRS score ≥20 at baseline. This double-blind, placebo-controlled trial compared two fixed doses of ABILIFY (10 or 30 mg/day) to placebo. The ABILIFY dose was started at 2 mg/day, which was titrated to 5 mg/day after 2 days, and to the target dose in 5 days in the 10 mg/day treatment arm, and in 13 days in the 30 mg/day treatment arm. Both doses of ABILIFY were superior to placebo in change from baseline to week 4 on the Y-MRS total score (Study 6 in Table 27).

### Table 26: Schizophrenia Studies

<table>
<thead>
<tr>
<th>Study Number</th>
<th>Treatment Group</th>
<th>Primary Efficacy Measure: PANSS</th>
<th>Mean Baseline Score (SD)</th>
<th>LS Mean Change from Baseline (SE)</th>
<th>Placebo-subtracted Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>ABILIFY (15 mg/day)*</td>
<td>98.5 (-15.5)</td>
<td>-12.6 (2.40)</td>
<td>(-18.9, -6.2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ABILIFY (30 mg/day)*</td>
<td>99.0 (-11.4)</td>
<td>-8.5 (2.39)</td>
<td>(-14.8, -2.1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>100.2 (2.9)</td>
<td>-2.9 (1.65)</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Study 2</td>
<td>ABILIFY (20 mg/day)*</td>
<td>92.6 (-14.5)</td>
<td>-9.6 (2.23)</td>
<td>(-15.4, -3.8)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ABILIFY (30 mg/day)*</td>
<td>94.2 (-13.9)</td>
<td>-9.0 (2.24)</td>
<td>(-14.8, -3.1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>94.3 (-5.0)</td>
<td>-5.0 (1.85)</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Study 3</td>
<td>ABILIFY (10 mg/day)*</td>
<td>92.7 (-15.0)</td>
<td>-12.7 (2.38)</td>
<td>(-19.0, -6.41)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ABILIFY (15 mg/day)*</td>
<td>93.2 (-11.7)</td>
<td>-9.4 (2.38)</td>
<td>(-15.7, -3.08)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ABILIFY (20 mg/day)*</td>
<td>92.5 (-14.4)</td>
<td>-12.1 (2.45)</td>
<td>(-18.5, -5.68)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>92.3 (-2.3)</td>
<td>-2.3 (2.35)</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Study 4</td>
<td>ABILIFY (2 mg/day)</td>
<td>90.7 (-8.2)</td>
<td>-2.9 (1.90)</td>
<td>(-8.29, -2.47)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ABILIFY (5 mg/day)</td>
<td>92.0 (-10.6)</td>
<td>-5.2 (1.35)</td>
<td>(-10.7, -0.19)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ABILIFY (10 mg/day)*</td>
<td>90.0 (-11.3)</td>
<td>-5.9 (1.88)</td>
<td>(-11.3, -0.58)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>90.8 (-5.3)</td>
<td>-5.3 (1.97)</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Study 5</td>
<td>(Pediatric, 10-17 years) ABILIFY (10 mg/day)*</td>
<td>93.6 (-26.7)</td>
<td>-5.5 (1.91)</td>
<td>(-10.7, -0.21)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ABILIFY (30 mg/day)*</td>
<td>94.0 (-28.6)</td>
<td>-7.4 (1.92)</td>
<td>(-12.7, -2.13)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>94.6 (-21.2)</td>
<td>-2.2 (1.93)</td>
<td>--</td>
<td></td>
</tr>
</tbody>
</table>

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

* Difference (drug minus placebo) in least-squares mean change from baseline.

Doses statistically significantly superior to placebo.

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

![Kaplan-Meier curve showing cumulative proportion of patients with relapse](image)

14.2 Bipolar Disorder

**Acute Treatment of Manic and Mixed Episodes**

**Adults**

**Monotherapy**

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

### Table 27: Bipolar Studies

<table>
<thead>
<tr>
<th>Study Number</th>
<th>Treatment Group</th>
<th>Primary Efficacy Measure: Y-MRS</th>
<th>Mean Baseline Score (SD)</th>
<th>LS Mean Change from Baseline (SE)</th>
<th>Placebo-subtracted Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>ABILIFY (30/15 mg/day)*</td>
<td>29.0 (5.9)</td>
<td>-12.52 (1.05)</td>
<td>(-7.90, -2.76)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>28.5 (4.6)</td>
<td>-7.19 (1.07)</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Study 2</td>
<td>ABILIFY (30/15 mg/day)*</td>
<td>27.8 (5.7)</td>
<td>-8.15 (1.23)</td>
<td>(-7.80, -1.80)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>29.1 (6.9)</td>
<td>-3.35 (1.22)</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Study 3</td>
<td>ABILIFY (15-30 mg/day)*</td>
<td>28.5 (5.6)</td>
<td>-12.64 (0.84)</td>
<td>(-5.75, -1.51)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>28.9 (5.9)</td>
<td>-9.01 (0.81)</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Study 4</td>
<td>ABILIFY (15-30 mg/day)*</td>
<td>28.0 (5.8)</td>
<td>-11.98 (0.80)</td>
<td>(-4.44, -0.11)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>28.3 (5.6)</td>
<td>-9.70 (0.83)</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Study 5</td>
<td>ABILIFY (15 or 30 mg/day)*</td>
<td>23.2 (5.7)</td>
<td>-13.31 (0.50)</td>
<td>(-2.29, -2.37)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>23.0 (4.9)</td>
<td>-10.70 (0.69)</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Study 6</td>
<td>ABILIFY (10 mg/day)</td>
<td>29.8 (6.5)</td>
<td>-14.2 (0.89)</td>
<td>(-8.49, -3.50)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>29.5 (6.3)</td>
<td>-6.5 (0.87)</td>
<td>(-10.7, -5.77)</td>
<td></td>
</tr>
</tbody>
</table>

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

* Difference (drug minus placebo) in least-squares mean change from baseline.

Doses statistically significantly superior to placebo.
Maintenance Treatment of Bipolar I Disorder

Monotherapy Maintenance Therapy
A maintenance trial was conducted in adult patients meeting DSM-IV criteria for bipolar I disorder with a recent manic or mixed episode who had been stabilized on open-label ABILIFY and who had maintained a clinical response for at least 6 weeks. The first phase of this trial was an open-label stabilization period in which inpatients and outpatients were clinically stabilized and then maintained on open-label ABILIFY (15 mg or 30 mg/day, with a starting dose of 30 mg/day) for at least 6 consecutive weeks. One hundred sixty-one outpatients were then randomized in a double-blind fashion, to either the same dose of ABILIFY they were on at the end of the stabilization and maintenance period or placebo and were then monitored for manic or depressive relapse. During the randomization phase, ABILIFY was superior to placebo on time to the number of combined affective relapses (manic plus depressive), the primary outcome measure for this study (Study 7 in Figure 7). A total of 55 mood events were observed during the double-blind treatment phase. Nineteen were from the ABILIFY group and 36 were from the placebo group. The number of observed manic episodes in the ABILIFY group (6) were fewer than that in the placebo group (19), while the number of depressive episodes in the ABILIFY group (9) was similar to that in the placebo group (11).

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

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

Adjunctive Maintenance Therapy
An adjunctive maintenance trial was conducted in adult patients meeting DSM-IV criteria for bipolar I disorder with a recent manic or mixed episode. Patients were initiated on open-label lithium (0.6 to 1.0 mEq/L) or valproate (50 to 125 mg/mL) at therapeutic serum levels, and remained on stable doses for 2 weeks. At the end of 2 weeks, patients demonstrating inadequate response (Y-MRS total score ≥16 and ≤35% improvement on the Y-MRS total score) to lithium or valproate received ABILIFY with a starting dose of 15 mg/day with the option to increase to 30 mg or reduce to 10 mg as early as day 4, as adjunctive therapy with open-label lithium or valproate. Prior to randomization, patients on the combination of single-blind ABILIFY and lithium or valproate were required to maintain stability (Y-MRS and MADRS total scores ≤12) for 12 consecutive weeks. Three hundred thirty-seven patients were then randomized in a double-blind fashion, to either the same dose of ABILIFY they were on at the end of the stabilization period or placebo plus lithium or valproate and were then monitored for manic, mixed, or depressive relapse for a maximum of 52 weeks. ABILIFY was superior to placebo on the primary endpoint, time from randomization to relapse to any mood event (Study 8 in Figure 8). A mood event was defined as hospitalization for a manic, mixed, or depressive episode, study discontinuation due to lack of efficacy accompanied by Y-MRS score >16 and/or a MADRS >16, or an SAE of worsening disease accompanied by Y-MRS score >16 and/or a MADRS >16. A total of 68 mood events were observed during the double-blind treatment phase. Twenty-five were from the ABILIFY group and 43 were from the placebo group. The number of observed manic episodes in the ABILIFY group (7) were fewer than that in the placebo group (19), while the number of depressive episodes in the ABILIFY group (14) was similar to that in the placebo group (18). The Kaplan-Meier curves of the time from randomization to relapse to any mood event during the 52-week, double-blind treatment phase for ABILIFY and placebo groups are shown in Figure 8.

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

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

The primary instrument used for assessing depressive symptoms was the Montgomery-Asberg Depression Rating Scale (MADRS), a 10-item clinician-rated scale used to assess the degree of depressive symptomatology. The key secondary instrument was the Sheehan Disability Scale (SDS), a 3-item self-rated instrument used to assess the impact of depression on three domains of functioning with each item scored from 0 (not at all) to 10 (extreme).

In the two trials (n=381, n=362), ABILIFY was superior to placebo in reducing mean MADRS total scores (Studies 1, 2 in Table 26). In one study, ABILIFY was also superior to placebo in reducing the mean SDS score.

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

An examination of population subgroups did not reveal evidence of differential response based on age, choice of prospective antidepressant, or race. With regard to gender, a smaller mean reduction on the MADRS total score was seen in males than in females.
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 compared with placebo. The mean daily dose of ABILIFY at the end of 8-week treatment was 8.6 mg/day (Study 1 in Table 29).

In the other 8-week, placebo-controlled trial in children and adolescents with autistic disorder (n=218), aged 6 to 17 years, three fixed doses of ABILIFY (5 mg/day, 10 mg/day, or 15 mg/day) were compared with 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 the 15 mg dose group, and after a third week, it was increased to 15 mg/day in the 15 mg treatment arm (Study 2 in Table 29). All three doses of ABILIFY significantly improved scores on the ABC-I subscale compared with placebo.

### Table 28: Adjunctive Treatment of Major Depressive Disorder Studies

<table>
<thead>
<tr>
<th>Study Number</th>
<th>Treatment Group</th>
<th>Primary Efficacy Measure: MADRS</th>
<th>Placebo-subtracted Differencea (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean Baseline Score (SD)</td>
<td>LS Mean Change from Baseline (SE)</td>
<td></td>
</tr>
<tr>
<td>Study 1</td>
<td>ABILIFY (5-20 mg/day)* + Antidepressant</td>
<td>25.2 (6.2)</td>
<td>-8.49 (0.66)</td>
</tr>
<tr>
<td></td>
<td>Placebo + Antidepressant</td>
<td>27.0 (5.5)</td>
<td>-5.65 (0.64)</td>
</tr>
<tr>
<td>Study 2</td>
<td>ABILIFY (5-20 mg/day)* + Antidepressant</td>
<td>26.0 (6.0)</td>
<td>-8.78 (0.63)</td>
</tr>
<tr>
<td></td>
<td>Placebo + Antidepressant</td>
<td>26.0 (6.5)</td>
<td>-5.77 (0.67)</td>
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</table>

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

<table>
<thead>
<tr>
<th>Study Number</th>
<th>Treatment Group</th>
<th>Primary Efficacy Measure: ABC-I</th>
<th>Placebo-subtracted Differencea (95% CI)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Mean Baseline Score (SD)</td>
<td>LS Mean Change from Baseline (SE)</td>
<td></td>
</tr>
<tr>
<td>Study 1</td>
<td>ABILIFY (2-15 mg/day)*</td>
<td>29.6 (6.37)</td>
<td>-12.9 (1.44)</td>
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<tr>
<td></td>
<td>Placebo</td>
<td>30.2 (6.52)</td>
<td>-5.0 (1.43)</td>
</tr>
<tr>
<td>Study 2</td>
<td>ABILIFY (5 mg/day)*</td>
<td>28.6 (7.56)</td>
<td>-12.4 (1.36)</td>
</tr>
<tr>
<td></td>
<td>ABILIFY (10 mg/day)*</td>
<td>28.2 (7.36)</td>
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<td></td>
<td>ABILIFY (15 mg/day)*</td>
<td>28.9 (8.41)</td>
<td>-14.4 (1.31)</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>28.0 (6.89)</td>
<td>-8.4 (1.39)</td>
</tr>
</tbody>
</table>

### 14.4 Irritability Associated with Autistic Disorder

**Pediatric Patients**

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

Efficacy was evaluated using two assessment scales: the Aberrant Behavior Checklist (ABC-I) subscale measured symptoms of irritability in autistic disorder to baseline and endpoint in the Irritability subscale of the ABC-I (ABC-I). The ABC-I subscale measured symptoms of irritability in autistic disorder.

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

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

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

### 14.6 Agitation Associated with Schizophrenia or Bipolar Mania

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

In a placebo-controlled trial in agitated inpatients predominantly meeting DSM-IV criteria for schizophrenia (n=350), four fixed ABILIFY injection doses of 1 mg, 5.25 mg, 9.75 mg, and 15 mg were evaluated. At 2 hours post-injection, the 5.25 mg, 9.75 mg, and 15 mg doses were statistically superior to placebo in the PANSS Excited Component (Study 1 in Table 31) and on the CGI-I Scale. In a second placebo-controlled trial in agitated inpatients predominantly meeting DSM-IV criteria for schizophrenia (n=445), one fixed ABILIFY injection dose of 9.75 mg was evaluated. At 2 hours post-injection, ABILIFY for injection was statistically superior to placebo in the PANSS Excited Component (Study 2 in Table 31) and on the CGI-I Scale. In a placebo-controlled trial in agitated inpatients meeting DSM-IV criteria for bipolar I disorder (manic or mixed) (n=291), two fixed ABILIFY injection doses of 9.75 mg and 15 mg were evaluated. At 2 hours post-injection, both doses were statistically superior to placebo in the PANSS Excited Component (Study 3 in Table 31).

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

### Table 30: Tourette's Disorder Studies (Pediatric)

<table>
<thead>
<tr>
<th>Study Number</th>
<th>Treatment Group</th>
<th>Primary Efficacy Measure: YGTSS TTS</th>
<th>Mean Baseline Score (SD)</th>
<th>LS Mean Change from Baseline (SE)</th>
<th>Placebo-subtracted Difference* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>ABILIFY (low dose)*</td>
<td>29.2 (5.63)</td>
<td>-13.4 (1.59)</td>
<td>-6.3 (-10.2, -2.3)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ABILIFY (high dose)*</td>
<td>31.2 (6.40)</td>
<td>-16.9 (1.61)</td>
<td>-9.9 (-13.8, -5.9)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>30.7 (5.95)</td>
<td>-7.1 (1.55)</td>
<td>--</td>
<td></td>
</tr>
</tbody>
</table>

### Table 31: Agitation Associated with Schizophrenia or Bipolar Mania Studies

<table>
<thead>
<tr>
<th>Study Number</th>
<th>Treatment Group</th>
<th>Primary Efficacy Measure: PANSS Excited Component</th>
<th>Mean Baseline Score (SD)</th>
<th>LS Mean Change from Baseline (SE)</th>
<th>Placebo-subtracted Difference* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 1</td>
<td>ABILIFY (1 mg)</td>
<td>19.16 (3.26)</td>
<td>-4.47 (0.72)</td>
<td>-1.19 (-2.96, 0.59)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ABILIFY (5.25 mg)*</td>
<td>19.41 (3.31)</td>
<td>-5.65 (0.68)</td>
<td>-2.37 (-4.10, -0.63)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ABILIFY (9.75 mg)*</td>
<td>19.42 (2.60)</td>
<td>-6.69 (0.72)</td>
<td>-3.40 (-5.18, -1.62)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ABILIFY (15 mg)*</td>
<td>19.34 (2.38)</td>
<td>-5.72 (0.72)</td>
<td>-2.44 (-4.21, -0.68)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>19.18 (2.95)</td>
<td>-3.28 (0.70)</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Study 2</td>
<td>ABILIFY (9.75 mg)*</td>
<td>18.82 (2.67)</td>
<td>-7.27 (0.59)</td>
<td>-2.48 (-3.77, -1.19)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>18.74 (2.71)</td>
<td>-4.78 (0.69)</td>
<td>--</td>
<td></td>
</tr>
</tbody>
</table>

### Table 32: ABILIFY Tablet Presentations

<table>
<thead>
<tr>
<th>Tablet Strength</th>
<th>Tablet Color/Shape</th>
<th>Tablet Markings</th>
<th>Pack Size</th>
<th>NDC Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 mg</td>
<td>green</td>
<td>“A-006” and “2”</td>
<td>Bottle of 30</td>
<td>59148-006-13</td>
</tr>
<tr>
<td>5 mg</td>
<td>blue</td>
<td>“A-007” and “5”</td>
<td>Bottle of 30</td>
<td>59148-007-13</td>
</tr>
<tr>
<td>10 mg</td>
<td>pink</td>
<td>“A-008” and “10”</td>
<td>Bottle of 30</td>
<td>59148-008-13</td>
</tr>
<tr>
<td>15 mg</td>
<td>yellow</td>
<td>“A-009” and “15”</td>
<td>Bottle of 30</td>
<td>59148-009-13</td>
</tr>
<tr>
<td>20 mg</td>
<td>white</td>
<td>“A-010” and “20”</td>
<td>Bottle of 30</td>
<td>59148-010-13</td>
</tr>
<tr>
<td>30 mg</td>
<td>pink</td>
<td>“A-011” and “30”</td>
<td>Bottle of 30</td>
<td>59148-011-13</td>
</tr>
</tbody>
</table>

### Table 33: ABILIFY DISCMELT Orally Disintegrating Tablet Presentations

<table>
<thead>
<tr>
<th>Tablet Strength</th>
<th>Tablet Color</th>
<th>Tablet Markings</th>
<th>Pack Size</th>
<th>NDC Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mg</td>
<td>pink</td>
<td>“A” and “640”</td>
<td>Blister of 30</td>
<td>59148-640-23</td>
</tr>
<tr>
<td>15 mg</td>
<td>yellow</td>
<td>“A” and “641”</td>
<td>Blister of 30</td>
<td>59148-641-23</td>
</tr>
</tbody>
</table>
ABILIFY® (aripiprazole) Oral Solution (1 mg/mL) is supplied in child-resistant bottles along with a calibrated oral dosing cup. ABILIFY Oral Solution is available as follows:

- 150 mL bottle NDC 59148-013-15
- 9.75 mg/1.3 mL (7.5 mg/mL) solution in clear, Type 1 glass vials as follows:
  - 9.75 mg/1.3 mL single-dose vial NDC 59148-016-65

16.2 Storage

**Tablets**

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

**Oral Solution**

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

**Injection**

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

17 PATIENT COUNSELING INFORMATION

**See Medication Guide**

**Discuss the following issues with patients prescribed ABILIFY:**

### Clinical Worsening of Depression and Suicide Risk

Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to look for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient’s prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient’s presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication [see WARNINGS AND PRECAUTIONS (5.3)].

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

### Pathological Gambling and Other Compulsive Behaviors

Advis patients and their caregivers of the possibility that they may experience compulsive urges to shop, intense urges to gamble, compulsive sexual urges, binge eating and/or other compulsive urges and the inability to control these urges while taking aripiprazole. In some cases, but not all, the urges were reported to have stopped when the dose was reduced or stopped [see WARNINGS AND PRECAUTIONS (5.7)].

---

**Use of Orally Disintegrating Tablet**

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

**Interference with Cognitive and Motor Performance**

Because ABILIFY may have the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that ABILIFY therapy does not affect them adversely [see WARNINGS AND PRECAUTIONS (5.12)].

**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 POPULATIONS (8.3)].

**Concomitant Medication**

Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions [see DRUG INTERACTIONS (7)].

**Heat Exposure and Dehydration**

Patients should be advised regarding appropriate care in avoiding overheating and dehydration [see WARNINGS AND PRECAUTIONS (5.13)].

**Sugar Content**

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

**Phenylketonurics**

Phenylalanine is a component of aspartame. Each ABILIFY DISCMELT Orally Disintegrating Tablet contains the following amounts: 10 mg, 1.12 mg phenylalanine and 15 mg, 1.68 mg phenylalanine. Tablets manufactured by Otsuka Pharmaceutical Co., Ltd., Tokyo, 101-8535 Japan;

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

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

ABILIFY is a trademark of Otsuka Pharmaceutical Company.

© 2017, Otsuka Pharmaceutical Co., Ltd., Tokyo, 101-8535 Japan
What is ABILIFY® (aripiprazole) Tablets, Orally Disintegrating Tablets, Oral Solution, and Injection, for intramuscular use

What is the most important information I should know about ABILIFY®?
(For other side effects, also see “What are the possible side effects of ABILIFY®?”)

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

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

• **Risk of suicidal thoughts or actions:** Antidepressant medicines, depression and other serious mental illnesses, and suicidal thoughts or actions:
  
  1. Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, and young adults within the first few months of treatment.
  
  2. Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a particularly high risk of having suicidal thoughts or actions. These include people who have (or have a family history of) bipolar illness (also called manic-depressive illness) or suicidal thoughts or actions.
  
  3. How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?
    
    • Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.
    
    • Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
    
    • Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare provider between visits as needed, especially if you have concerns about symptoms.

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

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

What else do I need to know about antidepressant medicines?

• Never stop an antidepressant medicine without first talking to a healthcare provider. Stopping an antidepressant medicine suddenly can cause other symptoms.

• **Antidepressants are medicines used to treat depression and other illnesses.** It is important to discuss all the risks of treating depression and also the risks of not treating it. Patients and their families or other caregivers should discuss all treatment choices with the healthcare provider, not just the use of antidepressants.

• **Antidepressant medicines have other side effects.** Talk to the healthcare provider about the side effects of the medicine prescribed for you or your family member.

• **Antidepressant medicines can interact with other medicines.** Know all of the medicines that you or your family member takes. Keep a list of all medicines to show the healthcare provider. Do not start new medicines without first checking with your healthcare provider.

• **Not all antidepressant medicines prescribed for children are FDA approved for use in children.** Talk to your child’s healthcare provider for more information.

What is ABILIFY®?

• **ABILIFY Oral Tablets, Orally-Disintegrating Tablets, and Oral Solution** are prescription medicines used to treat:
  
  o Schizophrenia
  
  o manic or mixed episodes that happen with bipolar I disorder
  
  o major depressive disorder (MDD) when ABILIFY® is used with antidepressant medicines
  
  o irritability associated with autistic disorder
  
  o Tourette’s disorder

• **ABILIFY Injection** is a prescription medicine used to treat:
  
  o agitation associated with schizophrenia or bipolar mania

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

• under 13 years of age with schizophrenia
• under 10 years of age with bipolar I disorder
• under 6 years of age with irritability associated with autistic disorder
• under 6 years of age with Tourette’s disorder
Do not take ABILIFY if you are allergic to aripiprazole or any of the ingredients in ABILIFY. See the end of this Medication Guide for a complete list of ingredients in ABILIFY.

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

Tell your healthcare provider about all the medicines that you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. ABILIFY and other medicines may affect each other causing possible serious side effects. ABILIFY may affect the way other medicines work, and other medicines may affect how ABILIFY works.

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

How should I take ABILIFY?
- Take ABILIFY exactly as your healthcare provider tells you to take it. Do not change the dose or stop taking ABILIFY yourself.
- ABILIFY can be taken with or without food.
- ABILIFY tablets should be swallowed whole.
- If you miss a dose of ABILIFY, take the missed dose as soon as you remember. If it is almost time for the next dose, just skip the missed dose and take your next dose at the regular time. Do not take two doses of ABILIFY at the same time.
- If you have been prescribed ABILIFY DISCMELT, take it as follows:
  - Do not open the blister until ready to take the DISCMELT tablet.
  - To remove one DISCMELT tablet, open the package and peel back the foil on the blister to expose the tablet.
  - Do not push the tablet through the foil because this could damage the tablet.
  - Immediately upon opening the blister, using dry hands, remove the tablet and place the entire ABILIFY DISCMELT Orally Disintegrating Tablet on the tongue.
  - Tablet disintegration occurs rapidly in saliva. It is recommended that ABILIFY DISCMELT be taken without liquid. However, if needed, it can be taken with liquid.
  - Do not attempt to split the DISCMELT tablet.
- If you take too much ABILIFY, call your healthcare provider or poison control center at 1-800-222-1222 right away, or go to the nearest hospital emergency room.

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

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

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

- Increased fat levels (cholesterol and triglycerides) in your blood.
- Weight gain. You and your healthcare provider should check your weight regularly.
- Unusual urges. Some people taking ABILIFY have had unusual urges, such as gambling, binge eating or eating that you cannot control (compulsive), compulsive shopping and sexual urges.
  If you or your family members notice that you are having unusual urges or behaviors, talk to your healthcare provider.
- Orthostatic hypotension (decreased blood pressure). Lightheadedness or fainting may happen when rising too quickly from a sitting or lying position.
- Low white blood cell count
- Seizures (convulsions)
- Problems with control of your body temperature especially when you exercise a lot or are in an area that is very hot.
  It is important for you to drink water to avoid dehydration. See “What should I avoid while receiving ABILIFY?”
- Difficulty swallowing that can cause food or liquid to get into your lungs.

The most common side effects of ABILIFY in adults include:

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

The most common side effects of ABILIFY in children include:

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

These are not all the possible side effects of ABILIFY. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store ABILIFY?

- Store ABILIFY at room temperature, between 68°F to 77°F (20°C to 25°C).
- Opened bottles of ABILIFY Oral Solution can be used for up to 6 months after opening, but not beyond the expiration date on the bottle.
- Keep ABILIFY and all medicines out of the reach of children.

General information about the safe and effective use of ABILIFY

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use ABILIFY for a condition for which it was not prescribed. Do not give ABILIFY to other people, even if they have the same symptoms you have. It may harm them. You can ask your healthcare provider or pharmacist for information about ABILIFY that was written for healthcare professionals.

What are the ingredients in ABILIFY?

Active ingredient: aripiprazole

Inactive ingredients:

Tablets: cornstarch, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, and microcrystalline cellulose. Colorants include ferric oxide (yellow or red) and FD&C Blue No. 2 Aluminum Lake

ABILIFY DISCMELT Orally Disintegrating Tablets: acesulfame potassium, aspartame (which contains phenylalanine), calcium silicate, croscarmellose sodium, crospovidone, crème de vanilla (natural and artificial flavors), magnesium stearate, microcrystalline cellulose, silicon dioxide, tartrazine, and xylitol. Colorants include ferric oxide (yellow or red) and FD&C Blue No. 2 Aluminum Lake

ABILIFY Oral Solution: disodium edetate, fructose (200 mg per mL), glycerin, dl-lactic acid, methylparaben, propylene glycol, propylparaben, sodium hydroxide, sucrose (400 mg per mL), and purified water. The oral solution is flavored with natural orange cream and other natural flavors

For more information about ABILIFY go to www.abilify.com or call 1-800-438-6055.

Tablets manufactured by Otsuka Pharmaceutical Co., Ltd., Tokyo, 101-8535 Japan
Orally Disintegrating Tablets, Oral Solution, and Injection manufactured by Bristol-Myers Squibb Company, Princeton, NJ 08543 USA
Distributed and marketed by Otsuka America Pharmaceutical, Inc., Rockville, MD 20850 USA

ABILIFY is a trademark of Otsuka Pharmaceutical Company.

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