The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to be increased by the duration of treatment and the overall dosage. The occurrence of tardive dyskinesia can be less common, after relatively brief treatment periods of 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cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn.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, may cause or exacerbate the clinical symptoms of tardive dyskinesia.

It is not clear whether the risk of tardive dyskinesia is related to the risk of antipsychotic-induced hyperprolactinemia. The risk of developing hyperprolactinemia appears to be increased in the presence of baseline hyperprolactinemia. Prolactin levels should be assessed before and periodically during antipsychotic treatment.

The risk of developing tardive dyskinesia is unknown for children and adolescents treated with antipsychotic drugs for any indication. The risk may be increased in children and adolescents with schizophrenia spectrum disorders who are treated with antipsychotic drugs for more than 1 year.

Angina pectoris - Antipsychotics may cause or exacerbate angina pectoris, hypertension, or ischemic heart disease. Symptomatic cardiac accelerated heart rate, hypertension, dyspnea, and other manifestations of coronary ischemia or ischemic heart disease may develop in patients treated with antipsychotics. Therefore, treatment with these compounds should be preceded by clinical evaluation and continued cardiac monitoring.

Dysphagia - Eosinophilic dysphagia, which may have an autoimmune basis, has been reported in patients treated with antipsychotics. The risk of developing eosinophilic dysphagia appears to be highest in elderly patients or patients with a history of eosinophilia.

Neuroleptic Malignant Syndrome (NMS) - A potentially fatal symptom complex sometimes referred to as neuroleptic malignant syndrome (NMS) has been described in patients treated with antipsychotics.

The following is a partial list of the more common symptoms reported to be associated with neuroleptic malignant syndrome (NMS): fever or hyperpyrexia; increased muscle tone; autonomic instability with fluctuating temperatures, blood pressure, and pulse; altered mental status ranging from confusion to aggressive behavior; severe agitation or restlessness; tachypnea or tachycardia; changes in mental status including disorientation, delirium, coma and other altered states; convulsions; hyperesthesia; and dehydration. The diagnosis of NMS should be considered in patients who present with any or all of these symptoms.

ACE Inhibitors - ACE inhibitors may cause or exacerbate angina pectoris, hypertension, or ischemic heart disease. Symptomatic cardiac accelerated heart rate, hypertension, dyspnea, and other manifestations of coronary ischemia or ischemic heart disease may develop in patients treated with ACE inhibitors. Therefore, treatment with these compounds should be preceded by clinical evaluation and continued cardiac monitoring.

SUICIDALITY AND ANTIDEPRESSANT DRUGS

Elderly patients with dementia-related psychosis treated with antipsychotics are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), 6707 patients, of antipsychotic drug treatment in the elderly with dementia showed a trend toward an increased mortality in patients treated with antipsychotics. The risk of mortality was elevated for all antipsychotic drug treatments compared to placebo. The increases observed were consistent with other studies of elderly patients in dementia and Alzheimer's disease treated with antipsychotics. The risk of mortality was highest within the first month of treatment and appeared to increase with duration of treatment. However, the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as compared to placebo, or to the characteristics of the patient populations treated.

Careful examination of the trials of atypical antipsychotics, which have been studied for a longer period of time, and which were not as severely demented and frail as those in the original NMS report, revealed an increased mortality rate but the numbers were not sufficient to reach any statistical significance.
Aripiprazole at doses of 10 mg/day to 30 mg/day for 14 days had no effect on dextromethorphan's O-dealkylation to its active metabolite, dehydro-aripiprazole, in healthy subjects. No dosage adjustment of aripiprazole is recommended when administered concomitantly with dextromethorphan.

Aripiprazole at doses between 10 mg/day to 30 mg/day for 14 days had no effect on the steady-state pharmacokinetics of valproate and O-desmethy lsertraline when these antidepressant therapies were coadministered with aripiprazole at doses between 10 mg/day to 30 mg/day. No change was observed in the pharmacokinetics of valproate or O-desmethy lsertraline when these antidepressant therapies were coadministered with aripiprazole at doses between 10 mg/day to 30 mg/day. No dosage adjustment of aripiprazole is recommended when administered concomitantly with valproate or O-desmethy lsertraline.

Ketoconazole and Other CYP3A4 Inhibitors: Both CYP3A4 and CYP2D6 are responsible for aripiprazole metabolism. Agents that induce CYP3A4 (eg, carbamazepine) could cause a five- to tenfold increase in the exposure of aripiprazole by inhibition of CYP3A4. Carbamazepine, when added to aripiprazole therapy, increased the AUC of aripiprazole by 112% but decreased the AUC of its active metabolite, dehydro-aripiprazole, by 35%. The clinical relevance of these changes is unknown. In healthy subjects, potent inhibitors of CYP2D6, increased the AUC of aripiprazole by 50%.

Drugs as inhibitors or inducers of these enzymes, or other factors, like smoking, is unlikely.

Drug interactions: Aripiprazole was associated with adverse reactions as defined in the trials adding aripiprazole to antidepressants. In one trial adding aripiprazole (15 mg/d) and an SSRI (paroxetine 20 mg/d) to the antidepressant therapy of 182 patients (mean age 42 years), subjects had no effect on the steady-state pharmacokinetics of valproate and O-desmethy lsertraline when these antidepressant therapies were coadministered with aripiprazole at doses between 10 mg/day to 30 mg/day. No dosage adjustment of aripiprazole is recommended when administered concomitantly with valproate or O-desmethy lsertraline.

Lithium: A pharmacokinetic interaction of aripiprazole with lithium is unlikely because lithium is not bound to plasma proteins, is not metabolized, and is not extensively excreted unchanged in urine. Concomitant administration of lithium and aripiprazole did not cause any clinically relevant changes in the pharmacokinetics of either drug. Although lithium and aripiprazole are both renally eliminated, no significant changes in the pharmacokinetics of either drug were observed. Lithium concentrations in subjects receiving aripiprazole were unchanged, and lithium concentrations did not change significantly in subjects receiving lithium alone.

Aripiprazole is not metabolized by CYP enzymes. Aripiprazole is metabolized by liver microsomal enzymes, primarily CYP3A4, and some CYP2D6, and is excreted unchanged in urine and feces. Oral aripiprazole is rapidly absorbed from the gastrointestinal tract, with peak plasma concentrations occurring after 1-4 hours.

Pediatric Use: Aripiprazole is not a substrate of CYP450. Carbamazepine (a potent CYP3A4 inhibitor) increased the AUC of aripiprazole in normal adults, but other strong CYP3A4 inhibitors did not change the AUC of aripiprazole. There are no adequate and well-controlled studies in pregnant women. Aripiprazole should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. The effect of aripiprazole on labor and delivery in humans is unknown.

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

Warnings and Precautions: Aripiprazole was administered in oral doses of 10 mg/day to 30 mg/day for 14 days to 151 healthy volunteers. Aripiprazole caused no clinically relevant changes in vital signs, orthostatic hypotension, or other cardiovascular parameters. Aripiprazole was associated with a median increase in heart rate of 2 beats per minute compared to no increase among placebo patients. Aripiprazole treatment was associated with an increased incidence of self-reported sweating and dizziness. The combination of adverse events as defined in Aventis Reactions reported by patients treated with oral aripiprazole at multiple doses 2.5 mg/day or higher during any phase of a trial within the database of 12,454 adult patients, oral aripiprazole excluding those events already listed as adverse events in other sections of this labeling. Aripiprazole was associated with an increased incidence of suicidal behavior and self-injurious behavior in children, adolescents, and young adults treated with antidepressants or antipsychotics. Patients treated with aripiprazole and who were reported to have a diagnosis of Not Otherwise Specified mood disorder exhibited a greater incidence of suicidal behavior, thoughts, and self-injury compared to patients treated with placebo. Aripiprazole should be used with caution in patients with a history of suicide or suicidal ideation.

Drug Abuse and Dependence: Long-term treatment with aripiprazole does not result in the development of dependence or tolerance. However, the long-term administration of antipsychotics can result in a pattern of drug-induced neuroleptic malignant syndrome-like adverse events. Antipsychotic-induced neuroleptic malignant syndrome-like adverse events have been reported in patients with a history of substance use disorder and prior neuroleptic use.

Intravenous Aripiprazole: Aripiprazole is not a substrate of CYP450. Quinidine and Other CYP2D6 Inhibitors: Aripiprazole is not a substrate of CYP450. The CYP2C19 and CYP2E1 enzymes. Aripiprazole also does not undergo direct glucuronidation. This suggests that an interaction of aripiprazole with other drugs that inhibit these enzymes is unlikely. This is supported by the results of in vitro studies and clinical experience with aripiprazole.

In the trials adding aripiprazole to antidepressants, patients first received 8 weeks of antidepressant treatment followed by 6 weeks of adjunctive therapy. The proportion of patients treated with aripiprazole with over-the-counter drugs, since there is a potential for interactions [see Drug Interactions]. The combination of adverse events as defined in Aventis Reactions reported by patients treated with oral aripiprazole at multiple doses 2.5 mg/day or higher during any phase of a trial within the database of 12,454 adult patients, oral aripiprazole excluding those events already listed as adverse events in other sections of this labeling. Aripiprazole was associated with an increased incidence of self-reported sweating and dizziness. Aripiprazole at doses of 10 mg/day to 30 mg/day for 14 days had no effect on dextromethorphan's O-dealkylation to its active metabolite, dehydro-aripiprazole, in healthy subjects. No dosage adjustment of aripiprazole is recommended when administered concomitantly with dextromethorphan.

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Ketoconazole and Other CYP3A4 Inhibitors: Both CYP3A4 and CYP2D6 are responsible for aripiprazole metabolism. Agents that induce CYP3A4 (eg, carbamazepine) could cause a five- to tenfold increase in the exposure of aripiprazole by inhibition of CYP3A4. Carbamazepine, when added to aripiprazole therapy, increased the AUC of aripiprazole by 112% but decreased the AUC of its active metabolite, dehydro-aripiprazole, by 35%. The clinical relevance of these changes is unknown. In healthy subjects, potent inhibitors of CYP2D6, increased the AUC of aripiprazole by 50%.
IMPORTANT SAFETY INFORMATION and INDICATION for ABILIFY® (aripiprazole)

**INDICATION**
- ABILIFY (aripiprazole) is indicated for use as an adjunctive therapy to antidepressants for the acute treatment of Major Depressive Disorder in adults

**IMPORTANT SAFETY INFORMATION**

**Increased Mortality in Elderly Patients with Dementia-Related Psychosis**
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk (1.6 to 1.7 times) of death compared to placebo (4.5% vs 2.6%, respectively). Although the causes of death were varied, most of the deaths appeared to be cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. ABILIFY is not approved for the treatment of patients with dementia-related psychosis.

**Suicidality and Antidepressant Drugs**
Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of adjunctive ABILIFY or another antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increased risk of suicidality in adults beyond age 24. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. ABILIFY is not approved for use in pediatric patients with depression.

See Full Prescribing Information for complete Boxed WARNINGS.

**Contraindication** - Known hypersensitivity reaction to ABILIFY.
Reactions have ranged from pruritus/urticaria to anaphylaxis.

**Cerebrovascular Adverse Events, Including Stroke** - Increased incidence of cerebrovascular adverse events (eg, stroke, transient ischemic attack), including fatalities, have been reported in clinical trials of elderly patients with dementia-related psychosis treated with ABILIFY.

**Neuroleptic Malignant Syndrome (NMS)** - As with all antipsychotic medications, a rare and potentially fatal condition known as NMS has been reported with ABILIFY. NMS can cause hyperthermia, muscle rigidity, diaphoresis, tachycardia, irregular pulse or blood pressure, cardiac dysrhythmia, and altered mental status. If signs and symptoms appear, immediate discontinuation is recommended.

**Tardive Dyskinesia (TD)** - The risk of developing TD and the potential for it to become irreversible may increase as the duration of treatment and the total cumulative dose increase. Prescribing should be consistent with the need to minimize TD. If signs and symptoms appear, discontinuation should be considered since TD may remit, partially or completely.

**Hyperglycemia and Diabetes Mellitus** - Hyperglycemia, in some cases associated with ketoadiposis, coma, or death, has been reported in patients treated with atypical antipsychotics including ABILIFY. Patients with diabetes should be monitored for worsening of glucose control; those with risk factors for diabetes should undergo baseline and periodic fasting blood glucose testing. Patients who develop symptoms of hyperglycemia should also undergo fasting blood glucose testing. There have been few reports of hyperglycemia with ABILIFY.

**Orthostatic Hypotension** - ABILIFY may be associated with orthostatic hypotension and should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or conditions which would predispose them to hypotension.

**Seizures/Convulsions** - As with other antipsychotic drugs, ABILIFY should be used with caution in patients with a history of seizures or with conditions that lower the seizure threshold.

**Potential for Cognitive and Motor Impairment** - Like other antipsychotics, ABILIFY may have the potential to impair judgment, thinking, or motor skills. Patients should not drive or operate hazardous machinery until they are certain ABILIFY does not affect them adversely.

**Body Temperature Regulation** - Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotics. Appropriate care is advised for patients who may exercise strenuously, be exposed to extreme heat, receive concomitant medication with anticholinergic activity, or be subject to dehydration.

**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 should be written for the smallest quantity consistent with good patient management in order to reduce the risk of overdose.

**Dysphagia** - Esophageal dysmotility and aspiration have been associated with antipsychotic drug use, including ABILIFY; use caution in patients at risk for aspiration pneumonia.

Physicians should advise patients to avoid alcohol while taking ABILIFY. Strong CYP3A4 (eg, ketoconazole) or CYP2D6 (eg, fluoxetine) inhibitors will increase ABILIFY drug concentrations; reduce ABILIFY dose by one-half when used concomitantly, except when used as adjunctive treatment with antidepressants in adults with Major Depressive Disorder.

CYP3A4 inducers (eg, carbamazepine) will decrease ABILIFY drug concentrations; double ABILIFY dose when used concomitantly.

**Commonly observed adverse reactions** (≥5% incidence and at least twice the rate of placebo for adjunctive ABILIFY vs adjunctive placebo, respectively):
- Adult patients (with Major Depressive Disorder): akathisia (25% vs 4%), restless leg syndrome (12% vs 2%), insomnia (8% vs 2%), constipation (5% vs 2%), fatigue (8% vs 4%), and blurred vision (6% vs 1%)

Dystonia is a class effect of antipsychotic drugs. Symptoms of dystonia may occur in susceptible individuals during the first days of treatment and at low doses.

Reference:
When adult patients have an inadequate response to antidepressant therapy

Taking the next step can help provide relief.

The first and only adjunctive therapy to antidepressants for Major Depressive Disorder in adults.

ABILIFY is indicated for use as an adjunctive therapy to antidepressants for the acute treatment of Major Depressive Disorder in adults.

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of Major Depressive Disorder and other psychiatric disorders. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior, especially during the initial few months of therapy, or at times of dose changes. ABILIFY is not approved for use in pediatric patients with depression (see Boxed WARNING).

Please see IMPORTANT SAFETY INFORMATION, including Boxed WARNINGS, on inside back cover.