

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

ARIPIPRAZOLE oral solution Initial U.S. Approval: 2002

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. Aripiprazole oral solution is not approved for the treatment of patients with dementia-related psychosis.

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) -----INDICATIONS AND USAGE--

Aripiprazole oral solution 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)
Irritability Associated with Autistic Disorder (14.4)
Treatment of Tourette's disorder (14.5)

		Initial Dose	Recommended Dose	Maximum Dose
Schizophrenia – a	dults (2.1)	10 to 15 mg/day	10 to 15 mg/day	30 mg/day
Schizophrenia – a	dolescents (2.1)	2 mg/day	10 mg/day	30 mg/day
Bipolar mania – a	dults: monotherapy (2.2)	15 mg/day	15 mg/day	30 mg/day
Bipolar mania – a	dults: adjunct to lithium or valproate (2.2)	10 to 15 mg/day	15 mg/day	30 mg/day
Bipolar mania – p adjunct to lithium	ediatric patients: monotherapy or as an or valproate (2.2)	2 mg/day	10 mg/day	30 mg/day
Irritability associa patients (2.4)	ted with autistic disorder – pediatric	2 mg/day	5 to 10 mg/day	15 mg/day
Tourette's	Patients < 50 kg	2 mg/day	5 mg/day	10 mg/day
disorder (2.5)	Patients ≥ 50 kg	2 mg/day	10 mg/day	20 mg/day

 Known CYP2D6 poor metabolizers: Half of the usual dose (2.7) -- DOSAGE FORMS AND STRENGTHS--

 Oral Solution: 1 mg/mL (3) ---CONTRAINDICATIONS

----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)
 Tardive Dyskinesia: Discontinue if clinically appropriate (5.5)

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

THOUGHTS AND BEHAVIORS WITH ANTIDEPRESSANT DRUGS INDICATIONS AND USAGE

DOSAGE AND ADMINISTRATION

Bipolar I Disorder rritability Associated with Autistic Disorder 2.5 Tourette's Disorder

Known hypersensitivity to aripiprazole oral solution (4)

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Pathological Gambling and Other Compulsive Behaviors 5.8 Orthostatic Hypotension 5.10 Leukopenia, Neutropenia, and Agranulocytosis 5.11 Seizures/Convulsions

with the prescriber [see Warnings and Precautions (5.3)].

Aripiprazole oral solution is indicated for the treatment of:
• Schizophrenia [see Clinical Studies (14.1)]

Irritability Associated with Autistic Disorder [see Clinical Studies (14.4)] Treatment of Tourette's Disorder [see Clinical Studies (14.5)]

5.12 Potential for Cognitive and Motor Impairment 5.13 Body Temperature Regulation 5.14 Suicide 5.15 Dysphagia

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FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 Schizophrenia

[see Clinical Studies (14.1)].

for maintenance treatment

Switching from Other Antipsychotics

administration should be minimized.

not been evaluated in clinical trials.

Pediatric Patients (6 to 17 years)

Pediatric Patients (6 to 18 years)

gradually at intervals of no less than 1 week.

week. [See Clinical Studies (14.5)].

Known CYP2D6 Poor Metabolizers

2.4 Irritability Associated with Autistic Disorde

2.2 Bipolar I Disorder

DRUG INTERACTIONS Drugs Having Clinically Important Interactions with Aripiprazole Oral Solution 7.2 Drugs Having No Clinically Important Interactions with Aripiprazole Oral Solution

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

THOUGHTS AND BEHAVIORS WITH ANTIDEPRESSANT DRUGS Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death.

Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term studies. These studies did not show an increase in the risk of suicidal thoughts and beh

antidepressant use in patients over age 24; there was a reduction in risk with antidepressant use in patients aged 65 and older (see Warnings and Precautions (5.3)).
In patients of all ages who are started on antidepressant therapy, monitor closely for worsening, and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication

Acute Treatment of Manic and Mixed Episodes associated with Bipolar I Disorder [see Clinical Studies (14.2)]

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

Maintenance Treatment: Maintenance of efficacy in schizophrenia was demonstrated in a trial involving patients with These patients were discontinued from those medications and randomized to either aripiprazole 15 mg/day or placebo, and

observed for relapse [see Clinical Studies (14.1)]. Patients should be periodically reassessed to determine the continued need

The recommended target dose of aripiprazole 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. Aripiprazole can be administered without regard to meals [see Clinical Studies (14.1)]. Patients should be periodically reassessed to determine the need for maintenance treatment.

There are no systematically collected data to specifically address switching patients with schizophrenia from other

antipsychotics to aripiprazole oral solution or concerning concomitant administration with other antipsychotics. While

immediate discontinuation of the previous antipsychotic treatment may be acceptable for some patients with schizophrenia

nore gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping antipsychotic

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. Aripiprazole oral solution can be given without regard to meals. The

recommended target dose of aripiprazole oral solution 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

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.

The recommended dosage range for the treatment of pediatric patients with irritability associated with autistic disorder is 5

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/ $^{\prime}$

day if needed. Dose adjustments of up to 5 mg/day should occur gradually, at intervals of no less than 1 week [see Clinical

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

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

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, aripiprazole oral solution dosage should then be adjusted to its original level.

When the coadministered CYP3A4 inducer is withdrawn, aripiprazole oral solution 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

Table 2: Dose Adjustments for Aripiprazole Oral Solution in Patients who are known CYP2D6 Poor Metabolizers and

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

Aripiprazole Oral Solution (1 mg/mL) is a clear, colorless to light yellow solution, supplied in child-resistant bottles along with

Aripiprazole oral solution is contraindicated in patients with a history of a hypersensitivity reaction to aripiprazole. Reactions

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

In three, 10-week, placebo-controlled studies of aripiprazole in elderly patients with psychosis associated with Alzheimer's

disease (n=938; mean age: 82.4 years; range: 56 to 99 years), the adverse reactions that were reported at an incidence of ≥3% and aripiprazole incidence at least twice that for placebo were lethargy [placebo 2%, aripiprazole 5%], somnolence (including

sedation) [placebo 3%, aripiprazole 8%], and incontinence (primarily, urinary incontinence) [placebo 1%, aripiprazole 5%]

The safety and efficacy of aripiprazole in the treatment of patients with psychosis associated with dementia have not been

established. If the prescriber elects to treat such patients with aripiprazole, assess for the emergence of difficulty swallowing

5.2 Gerebrovascular 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 aripiprazole -treated patients (mean age: 84 years; range: 78 to 88 years). In the fixed-dose study, there was a statistically

significant dose response relationship for cerebrovascular adverse events in patients treated with aripiprazole. Aripiprazole is

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/

or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has

been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term, placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and

behavior (suicidality) in children, adolescents, and young adults (ages 18 to 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

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia

antidepressants for MDD as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated

ss), hypomania, and mania, have been reported in adult and pediatric patients being treated with

(drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 5.

Increases Compared to Placebo

Decreases Compared to Placebo

14 additional cases

of drug therapy, or at times of dose changes, either increases or decreases.

18 to 24

25 to 64

-}<-

reach any conclusion about drug effect on suicide.

Dosage Adjustments for Aripiprazole Oral Solution

Administer half of usual dose

Administer half of usual dose

Administer a quarter of usual dose

Administer a quarter of usual dose

Patients Taking Concomitant CYP2D6 Inhibitors, 3A4 Inhibitors, and/or CYP3A4 Inducers

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

Studies (14.4)]. Patients should be periodically reassessed to determine the continued need for maintenance treatm

Aripiprazole oral solution can be given without regard to meals [see Clinical Studies (14.2)].

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

2.7 Dosage Adjustments for Cytochrome P450 Considerations

Factors

Known CYP2D6 Poor Metabolizers taking concomitant strong

Strong CYP2D6 (e.g., quinidine, fluoxetine, paroxetine) or CYP3A4

tablets should receive 25 mg of the solution [see Clinical Pharmacology (12.3)].

have ranged from pruritus/urticaria to anaphylaxis [see Adverse Reactions (6.2)].

5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

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

excessive salivation [placebo 0%, aripiprazole 4%], and lightheadedness [placebo 1%, aripiprazole 4%].

not approved for the treatment of patients with dementia-related psychosis [see Boxed Warning].

 $5.3 \quad \text{Suicidal Thoughts and Behaviors in Children, Adolescents, and Young Adults}$

essive somnolence, which could predispose to accidental injury or aspiration [see Boxed Warning].

CYP3A4 inhibitors (e.g., itraconazole, clarithromycin)

Strong CYP3A4 inducers (e.g., carbamazepine, rifampin)

inhibitors (e.g., itraconazole, clarithromycin)

Strong CYP2D6 and CYP3A4 inhibitors

3 DOSAGE FORMS AND STRENGTHS

5 WARNINGS AND PRECAUTIONS

a calibrated oral dosing cup.

4 CONTRAINDICATIONS

Aripiprazole oral solution is not approved for the treatment of patients with dementia-related psychosis [see Warn and Precautions (5.1)].

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

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

Metabolic Changes: Atypical antipsychotic drugs have been associated with metabolic changes that include

hyperglycemia/diabetes mellitus; dyslipidemia, and body weight gain (5.6)

Hyperglycemia/Diabetes Mellitus; Monitor glucose regularly in patients with and at risk for diabetes (5.6)

Dyslipidemia: Undesirable alterations in lipid levels have been observed in patients treated with atypical

Weight Gain: Weight gain has been observed with atypical antipsychotic use. Monitor weight (5.6)

Pathological Gambling and Other Compulsive Behaviors: Consider dose reduction or discontinuation (5.7)

Orthostatic Hypotension: Monitor heart rate and blood pressure and warn patients with known cardiovascular or

cerebrovascular disease, and risk of dehydration or syncope (5.8)

Leukopenia, Neutropenia, and Agranulocytosis: have been reported with antipsychotics including aripiprazole oral solution. Patients with a history of a clinically significant low white blood cell count (WBC) or a drug-induced leukopenia/ neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy

and discontinuation of aripiprazole oral solution should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors (5.10)

Seizures/Convulsions: Use cautiously in patients with a history of seizures or with conditions that lower the seizure

Potential for Cognitive and Motor Impairment: Use caution when operating machinery (5.12)

Suicide: The possibility of a suicide attempt is inherent in schizophrenia and bipolar disorder. Closely supervise high-risk

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
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,

To report SUSPECTED ADVERSE REACTIONS, contact Hetero Labs Limited at 1-866-495-1995 or FDA at 1-800-FDA-1088

-- DRUG INTERACTIONS

-----USE IN SPECIFIC POPULATIONS---

Pregnancy: May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure (8.1) Lactation: Monitor the breastfed infant for dehydration and lack of appropriate weight gain (8.2).

Dosage Adjustments for Aripiprazole oral solution

Normal to High

HDL Cholesterol

Normal to Low (≥40 mg/dL to <40 mg/dL)

(<150 mg/dL to ≥200 mg/dL)

Administer half of usual dose

Administer half of usual dose

Administer a quarter of usual dose

Double usual dose over 1 to 2 weeks

--ADVERSE REACTIONS--

Commonly observed adverse reactions (incidence ≥5% and at least twice that for placebo) were (6.1):

Known CYP2D6 Poor Metabolizers and strong CYP3A4 inhibitors | Administer a guarter of usual dose

antipsychotics (5.6)

Adult patients with schizophrenia: akathisia

Dosage adjustment due to drug interactions (7.1):

Known CYP2D6 Poor Metabolizers

Strong CYP2D6 or CYP3A4 inhibitors

Strong CYP2D6 and CYP3A4 inhibitors

Strong CYP3A4 inducers

Pregnancy 8.1 Pregnancy 8.2 Lactation

Pediatric Use

Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance9.2 Abuse

Human Experience

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14.4 Irritability Associated with Autistic Disorder

9.3 Dependence

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11 DESCRIPTION

8.6 CYP2D6 Poor Metabolizers

Hepatic and Renal Impairment 8.8 Other Specific Populations

Factors

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

threshold (5.11)

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 aripiprazole should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. Screening Patients for Bipolar Disorder: A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an

antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, It should be noted that aripiprazole 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 aripiprazole. Rare cases of NMS occurred during aripiprazole treatment in the worldwide clinical database. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and

evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia) Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology. The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious

medical problems for which specific treatments are available. There is no general agreement about specific pharmacological reatment 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 A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic

drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown. The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. Tardive dyskinesia may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, vever, 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, aripiprazole should be prescribed in a manner that is most likely to minimize the occurrence of ardive 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 aripiprazole, drug discontinuation should be considered. However, some patients may require treatment with aripiprazole 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, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. There have been reports of hyperglycemia in patients treated with aripiprazole [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 aripiprazole was not marketed at the time these studies were performed, it is not known if aripiprazole 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.

In an analysis of 13 placebo-controlled monotherapy trials in adults, primarily with schizophrenia or bipolar disorder, the mean change in fasting glucose in aripiprazole-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 aripiprazole-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

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

Category Change (at least once) Aripiprazole oral solution 31/822 3.8 Normal to High $(<100 \text{ mg/dL to} \ge 126 \text{ mg/dL})$ Placebo 22/605 3.6 31/176 17.6 Borderline to High (\geq 100 mg/dL and <126 mg/dL to \geq 126 mg/dL) Aripiprazole oral solution

Placebo 13/142 9.2 At 24 weeks, the mean change in fasting glucose in aripiprazole-treated patients was not significantly different than in placebotreated patients [+2.2 mg/dL (n=42) and +9.6 mg/dL (n=28), respectively]. 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 aripiprazole-treated patients (+4.8 mg/dL; with a

median exposure of 43 days; N=259) was not significantly different than in placebo-treated patients (+1.7 mg/dL; with a median exposure of 42 days; N=123). In an analysis of two placebo-controlled trials in pediatric and adolescent patients with irritability associated with autistic disorder (6 to 17 years) with median exposure of 56 days, the mean change in fasting glucose in aripiprazole-treated patients (-0.2 mg/dL; N=83) was not significantly different than in placebo-treated patients (-0.6 mg/dL; N=33). In an analysis of two placebo-controlled trials in pediatric and adolescent patients with Tourette's disorder (6 to 18 years) with median exposure of 57 days, the mean change in fasting glucose in aripiprazole-treated patients (0.79 mg/dL; N=90) was not significantly different than in placebo-treated patients (-1.66 mg/dL; N=58). 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 to 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 year) with Tourette's Disorder (median exposure 57 days)

Table 8: Changes in Fasting Glucose From Placebo-Controlled Trials in Pediatric and Adolescent Patients Category Change Indication Treatment Arm n/N % 2/236 8.0 Pooled Schizophrenia and Aripiprazole oral solution Bipolar Disorder Fasting Glucose 0/73 Normal to High Irritability Associated (<100 mg/dL to with Autistic Disord Placebo 0/32 0 ≥126 mg/dL) 3/88 Tourette's Disorder 1/58 1.7 Placebo Aripiprazole oral solution ooled Schizophrenia and 1/22 4.5 Bipolar Disorder Placebo 0/12 **Fasting Glucose** Borderline to High (≥100 mg/dL and 0/9 0 Aripiprazole oral solution **Autistic Disorder** 0/1 0 Placebo <126 mg/dL to ≥126 mg/dL) 0/11 Aripiprazole oral solution 0/4

At 12 weeks in the pooled adolescent schizophrenia and pediatric bipolar disorder trials, the mean change in fasting glucose mg/dL (n=15), respectively].

There were no significant differences between aripiprazole- 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/

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 placeho-treated patients with baseline normal fasting LDL measurements, who had median reatment 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 9 shows the proportion of adult patients, primarily from pooled schizophrenia and bipolar disorder monotherapy

		,	,-
Total Cholesterol Normal to High	Aripiprazole oral solution	34/1357	2.5
(<200 mg/dL to≥240 mg/dL)	Placebo	27/973	2.8
Fasting Triglycerides Normal to High	Aripiprazole oral solution	40/539	7.4
(<150 mg/dL to≥200 mg/dL)	Placebo	30/431	7.0
Fasting LDL Cholesterol Normal to High	Aripiprazole oral solution	2/332	0.6
(<100 mg/dL to≥160 mg/dL)	Placebo	2/268	0.7
HDL Cholesterol	Aripiprazole oral solution	121/1066	11.4
Normal to Low (≥40 mg/dL to<40 mg/dL)	Placebo	99/794	12.5
In monotherapy trials in adults, the proposition to the control of	ting triglycerides, and fasting LDL ks, Total Cholesterol (fasting/nonfa 5%); Fasting LDL Cholesterol, 0/34	cholesterol were similar asting), 1/71 (1.4%) vs. (0%) vs. 1/25 (4.0%), r	between aripiprazole 3/74 (4.1%); Fasting respectively; and at 24

(25%); Fasting LDL Cholesterol, 0/22 (0%) vs. 1/18 (5.6%), respectively. 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 11: Changes in Blood Lipid Parameters From Placebo-Controlled Monotherapy Trials in Pediatric and Adolescent Patients in Schizophrenia and Bipolar Disorder Treatment Arm n/N Total Cholesterol Aripiprazole oral soluti 3/220 1.4 (<170 mg/dL to ≥200 mg/dL) Placebo 0/116 0 Fasting Triglycerides Aripiprazole oral solution 7/187 3.7 Placeho 4/85 4.7 (<150 mg/dL to ≥200 mg/dL) HDL Cholesterol 27/236 11.4 Aripiprazole oral solution Normal to Low (≥40 mg/dL to <40 mg/dL) Placebo 22/109 20.2 In monotherapy trials of adolescents with schizophrenia and pediatric patients with bipolar disorder, the proportion of patients at 12 weeks and 24 weeks with changes from Normal to High in total cholesterol (fasting/nonfasting), fasting triglycerides, and fasting LDL cholesterol were similar between aripiprazole- and placebo-treated patients: at 12 weeks, Total Cholesterol (fasting/nonfasting), 0/57 (0%) vs. 0/15 (0%); Fasting Triglycerides, 2/72 (2.8%) vs. 1/14 (7.1%), respectively; and at 24

veeks, Total Cholesterol (fasting/nonfasting), 0/36 (0%) vs. 0/12 (0%); Fasting Triglycerides, 1/47 (2.1%) vs. 1/10 (10.0%), 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.

Table 12: Changes in Blood Lipid Parameters From Placebo-Controlled Trials in Pediatric Patients with Autistic Disorder Treatment Arm Total Cholesterol Aripiprazole oral solution 1/95 1.1 rmal to High (<170 mg/dL to ≥200 mg/dL) Placebo 0/34 0/75 Fasting Triglycerides Aripiprazole oral solution 0 Normal to High Placebo 0/30 0 <150 mg/dL to ≥200 mg/dL) HDL Cholesterol 9/107 8.4 Aripiprazole oral solution Normal to Lov Placebo 10.2 5/49 (≥40 mg/dL to <40 mg/dL)

Table 13 shows the proportion of patients with changes in total cholesterol (fasting/nonfasting) and fasting triglycerides (median exposure 57 days) and HDL cholesterol (median exposure 57 days) from two placebo-controlled trials in pediatric patients (6 to 18 years) with Tourette's Disorder. Table 13: Changes in Blood Lipid Parameters From Placebo-Controlled Trials in Pediatric Patients with Tourette's Disorder Treatment Arm n/N % Total Cholesterol (<170 mg/dL to ≥200 mg/dL) Placebo 0/46 Fasting Triglycerides 5/94 5.3 Aripiprazole oral solution

2/55

4/108

3.6

3.7

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

Aripiprazole oral solution

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 aripiprazole-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 aripiprazole-treated patients was -1.5 kg (n=73) compared to -0.2 kg (n=46) in placebo-treated patients. Table 14 shows the percentage of adult patients with weight gain $\geq\!\!7\%$ of body weight by indication.

Table 14: Percentage of Patients From Placebo-Controlled Trials in Adult Patients with Weight Gain ≥7% of Body Weight

n (%) Aripiprazole oral solution 852 69 (8.1) Schizophrenia 379 12 (3.2) Placebo Weight gain ≥7% of body weigh 719 16 (2.2) Aripiprazole oral solution Bipolar Mania[†] Placebo 598 16 (2.7) *4 to 6 weeks duration. †3 weeks duration

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

Table 15 shows the percentage of pediatric and adolescent patients with weight gain \geq 7% of body weight by indication. Table 15: Percentage of Patients From Placebo-Controlled Monotherapy Trials in Pediatric and Adolescent Patients with Weight Gain ≥7% of Body Weight

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

	Indication	Treatment Arm	N	Patients n (%)
	Pooled Schizophrenia and	Aripiprazole oral solution	381	20 (5.2)
	Bipolar Mania*	Placebo	187	3 (1.6)
Weight gain > 70/ of hady weight	Irritability Associated with Autistic Disorder [†]	Aripiprazole oral solution	209	55 (26.3)
Weight gain ≥7% of body weight		Placebo	98	7 (7.1)
	Touratta's Disordert	Aripiprazole oral solution	105	21 (20.0)
	Tourette's Disorder‡	Placebo	66	5 (7.6)
* 4 to 6 weeks duration. † 8 weeks of	duration. ‡8 to 10 weeks durat	tion.		

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 aripiprazole. 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 comparisons to age- and gender-matched population standards. A z-score change <0.5 SD is considered not clinically significant. After 26 weeks, the mean change in z-score was 0.09 SD. In an open-label trial that enrolled patients from two short-term, placebo-controlled trials, patients (6 to 17 years) with irritability associated with autistic disorder, as well as de novo patients, 60.3% (199/330) completed one year of therapy with ripiprazole. 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.

Aripiprazole may cause orthostatic hypotension, perhaps due to its α_1 -adrenergic receptor antagonism. The incidence of orthostatic hypotension-associated events from short-term, placebo-controlled trials of adult patients on oral aripiprazole (n=2467) included (aripiprazole incidence, placebo incidence) orthostatic hypotension (1%, 0.3%), postural dizziness (0.5%, 0.5%, 0.3%), and syncope (0.5%, 0.4%); of pediatric patients 6 to 18 years of age (n=732) on oral aripiprazole included orthostatic hypotension (1%, 0.3%), postural dizziness (0.5%, 0.3%), and syncope (0.5%, 0.4%); of pediatric patients 6 to 18 years of age (n=732) on oral aripiprazole included orthostatic hypotension (0.5%, 0%), postural dizziness (0.4%, 0%), and syncope (0.2%, 0%) [see Adverse Reactions (6.1)]. The incidence of a significant orthostatic change in blood pressure (defined as a decrease in systolic blood pressure \geq 20 mmHg accompanied by an increase in heart rate ≥ 25 bpm when comparing standing to supine values) for aripiprazole was not meaningfully different from placebo (aripiprazole incidence, placebo incidence): in adult oral aripiprazole-treated patients (4%, 2%), in pediatric oral aripiprazole-treated patients aged 6 to 18 years (0.4%, 1%). Aripiprazole should be used with caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease, or conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications) [see Drug

5.9 Falls Antipsychotics, including aripiprazole, 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 aripiprazole. Agranulocytosis has also been reported Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC)/absolute neutrophil count (ANC) and history of drug-induced leukopenia/neutropenia. In patients with a history of a clinically significant low WBC/ ANC or drug-induced leukopenia/neutropenia, perform a complete blood count (CBC) frequently during the first few months of therapy. In such patients, consider discontinuation of aripiprazole 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 aripiprazole in patients with severe neutropenia (absolute neutrophil count <1000/mm³) and follow their WBC counts until recovery. In short-term, placebo-controlled trials, patients with a history of seizures excluded seizures/convulsions occurred in 0.1%

(3/2467) of undiagnosed adult patients treated with oral aripiprazole, in 0.1% (1/732) of pediatric patients (6 to 18 years). As with other antipsychotic drugs, aripiprazole should be used cautiously in patients with a history of seizures or with conditions that lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in a population 5.12 Potential for Cognitive and Motor Impairment

Aripiprazole, like other antipsychotics, may have the potential to impair judgment, thinking, or motor skills. For example, in short-term, placebo-controlled trials, somnolence (including sedation) was reported as follows (aripiprazole incidence placebo incidence): in adult patients (n=2467) treated with oral aripiprazole (11%, 6%), in pediatric patients ages 6 to 1. (n=611) (24%, 6%). Somnolence (including sedation) led to discontinuation in 0.3% (8/2467) of adult patients and 3% (20/732) of pediatric patients (6 to 18 years) on oral aripiprazole in short-term, placebo-controlled trials. Despite the relatively modest increased incidence of these events compared to placebo, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that therapy with aripiprazole does

is advised when prescribing aripiprazole for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, (e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration) [see Adverse Reactions (6.2)]. The possibility of a suicide attempt is inherent in psychotic illnesses, bipolar disorder, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for aripiprazole should be written for the smallest quantity consistent

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care

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 aripiprazole. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. Aripiprazole and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia [see Warnings and Precautions (5.1) and Adverse Reactions (6.2)].

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

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 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/Convulsions [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,

The most common adverse reactions in the pediatric clinical trials (>10%) were somnolence, headache, vomiting Aripiprazole has been evaluated for safety in 13,543 adult patients who participated in multiple-dose, clinical trials in schizophrenia, bipolar disorder, another indication, Dementia of the Alzheimer's type, Parkinson's disease, and alcoholism, and who had approximately 7619 patient-years of exposure to oral aripiprazole. A total of 3390 patients were treated with oral aripiprazole for at least 180 days and 1933 patients treated with oral aripiprazole had at least 1 year of exposure. in schizophrenia, bipolar mania, autistic disorder, or Tourette's disorder and who had approximately 1,342 patient-years of exposure to oral aripiprazole. A total of 959 pediatric patients were treated with oral aripiprazole for at least 180 days and 556 pediatric patients treated with oral aripiprazole had at least 1 year of exposure. The conditions and duration of treatment with aripiprazole included (in overlapping categories) double-blind, comparative and noncomparative open-label studies, inpatient and outpatient studies, fixed- and flexible-dose studies, and short- and 6.1 Clinical Trials Experience

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

Commonly Observed Adverse Reactions he only commonly observed adverse reaction associated with the use of aripiprazole in patients with schizophrenia (incidence of 5% or greater and aripiprazole incidence at least twice that for placebo) was akathisia (aripiprazole 8%; placebo 4%). Adult Patients with Bipolar Mania wing findings are based on a pool of 3-week, placebo-controlled, bipolar mania trials in which oral aripiprazole was

administered at doses of 15 or 30 mg/day. Commonly observed adverse reactions associated with the use of aripiprazole in patients with bipolar mania (incidence of 5% or greater and aripiprazole incidence at least twice that for placebo) are shown in Table 16.

Table 16: Commonly Observed Adverse Reactions in Short-Term. Placebo-Controlled Trials of Adult Patients with Bipolar Mania Treated with Oral Aripiprazole Monotherapy Percentage of Patients Reporting Reaction

Preferred Term (n=917) (n=753) Akathisia 13 Sedation Restlessness Extrapyramidal Disorder Less Common Adverse Reactions in Adults Table 17 enumerates the pooled incidence, rounded to the pearest percent, of adverse reactions that occurred during acute

therapy (up to 6 weeks in schizophrenia and up to 3 weeks in bipolar mania), including only those reactions that occurred in 2% or more of patients treated with aripiprazole (doses ≥2 mg/day) and for which the incidence in patients treated with aripiprazole was greater than the incidence in patients treated with placebo in the combined dataset Table 17: Adverse Reactions in Short-Term, Placebo-Controlled Trials in Adult Patients Treated with Oral Aripiprazole

Percentage of Patients Reporting Reaction System Organ Class Preferred Term (n=1166)(n=1843)

	Percentage of Patients Reporting Reaction		
System Organ Class	Aripiprazole Oral Solution	Placebo	
Preferred Term	(n=1843)	(n=1166)	
Gastrointestinal Disorders			
Nausea	15	11	
Constipation	11	7	
Vomiting	11	6	
Dyspepsia	9	7	
Dry Mouth	5	4	
Toothache	4	3	
Abdominal Discomfort	3	2	
Stomach Discomfort	3	2	
General Disorders and Administration Site Conditi	ions		
Fatigue	6	4	
Pain	3	2	
Musculoskeletal and Connective Tissue Disorders			
Musculoskeletal Stiffness	4	3	
Pain in Extremity	4	2	
Myalgia	2	1	
Muscle Spasms	2	1	
Nervous System Disorders			
Headache	27	23	
Dizziness	10	7	
Akathisia	10	4	
Sedation	7	4	
Extrapyramidal Disorder	5	3	
Tremor	5	3	
Somnolence	5	3	
Psychiatric Disorders			
Agitation	19	17	
Insomnia	18	13	
Anxiety	17	13	
Restlessness	5	3	
Respiratory, Thoracic, and Mediastinal Disorders	,		
Pharyngolaryngeal Pain	3	2	
Cough	3	2	
*Adverse reactions reported by at least 2% of patien incidence equal to or less than placebo.	ts treated with oral aripiprazole, excep	t adverse reactions which had an	

An examination of population subgroups did not reveal any clear evidence of differential adverse reaction incidence on the 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 aripiprazole was administered at doses of 15 or 30 mg/day as adjunctive therapy with lithium or valproate

Adverse Reactions Associated with Discontinuation of Treatment In a study of patients who were already tolerating either lithium or valproate as monotherapy, discontinuation rates due to adverse reactions were 12% for patients treated with adjunctive aripiprazole compared to 6% for patients treated with adjunctive placebo. The most common adverse drug reactions associated with discontinuation in the adjunctive aripiprazoletreated 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 aripiprazole and lithium or valproate in patients with bipolar mania (incidence of 5% or greater and incidence at least twice that for adjunctive placebo) were: akathisia, insomnia,

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 aripiprazole (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

	Percentage of Patients Reporting Reaction			
System Organ Class	Aripiprazole Oral Solution + Li or Val†	Placebo + Li or Val		
Preferred Term	(n=253)	(n=130)		
Gastrointestinal Disorders				
Nausea	8	5		
Vomiting	4	0		
Salivary Hypersecretion	4	2		
Dry Mouth	2	1		
Infections and Infestations				
Nasopharyngitis	3	2		
Investigations				
Weight Increased	2	1		
Nervous System Disorders				
Akathisia	19	5		
Tremor	9	6		
Extrapyramidal Disorder	5	1		
Dizziness	4	1		
Sedation	4	2		
Psychiatric Disorders				
Insomnia	8	4		
Anxiety	4	1		
Restlessness	2	1		
*Adverse reactions reported by at least 2% of incidence equal to or less than placebo. † Lithium or Valproate	patients treated with oral aripiprazole, excep	t adverse reactions which		

Pediatric Patients (13 to 17 years) with Schizophrenia ngs are based on one 6-week, placebo-controlled trial in which oral aripiprazole was administered in doses

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

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

Pediatric Patients (10 to 17 years) with Bipolar Mania
The following findings are based on one 4-week, placebo-controlled trial in which oral aripiprazole 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 aripiprazole -treated and placebo-treated pediatric patients (10 to 17 years) was 7% and 2%, respectively.

Commonly observed adverse reactions associated with the use of aripiprazole in pediatric patients with bipolar mania (incidence of 5% or greater and aripiprazole 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 Aripiprazole

Percentage of Patients Reporting Reaction **Aripiprazole Oral Solution** Placebo Preferred Term (n=197)(n=97)Extrapyramidal Disorde 20 Fatigue Nausea Akathisia 10 lurred Vision Salivary Hypersecretion

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

The incidence of discontinuation due to adverse reactions between aripiprazole -treated and placebo-treated pediatric patients (6 to 17 years) was 10% and 8%, respectively. Commonly Observed Adverse Reactions Commonly observed adverse reactions associated with the use of aripiprazole in pediatric patients with autistic disorder

(incidence of 5% or greater and aripiprazole 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 Aripiprazole Percentage of Patients Reporting Reaction Aripiprazole oral solution Placebo (n=212)(n=101)Preferred Term Fatique omnolence 10 yrexia Drooling ecreased Appetite Salivary Hypersecretion Extrapyramidal Disorder

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 aripiprazole 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 aripiprazole -treated and placebo-treated pediatric patients (6 to 18 years) was 7% and 1%, respectively.

Lethargy

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

nly Observed Adverse Reactions in Short-Term, Placebo-Controlled Trials of Pediatric Patients (6 to 18 vears) with Tourette's Disorder Treated with Oral Aripiprazole Percentage of Patients Reporting Reaction Aripiprazole Oral Solution Placebo

(n=72)Sedation 13 13 Nausea Headache 10 **Vasopharyngitis** Fatigue Increased Appetite Less Common Adverse Reactions in Pediatric Patients (6 to 18 years) with Schizophrenia, Bipolar Mania, Autistic Disorder,

or Tourette's <u>Disorder</u>
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 Tourette's disorder), including only those reactions that occurred in 2% or more of pediatric paties aripiprazole (doses ≥2 mg/day) and for which the incidence in patients treated with aripiprazole was greater than the incidence in patients treated with placebo Table 22: Adverse Reactions in Short-Term, Placebo-Controlled Trials of Pediatric Patients (6 to 18 years) Treated with

Percentage of Patients Reporting Reaction

Preferred Term (n=370)(n=732)**Fve Disorders** Blurred Vision **Gastrointestinal Disorders**

dastrollitestillai Disorders				
Abdominal Discomfort		2	1	
Vomiting		8	7	
Nausea		8	4	
Diarrhea	ırrhea		3	
Salivary Hypersecretion		4	1	
Abdominal Pain Upper		3	2	
Constipation		2	2	
General Disorders and Administration	on Site Conditions			
Fatigue		10	2	
Pyrexia		4	1	
Irritability	2 1		1	
Asthenia		2	1	
Infections and Infestations			·	
Nasopharyngitis		6	3	
Investigations				
Weight Increased		3	1	
Metabolism and Nutrition Disorders			•	
Increased Appetite		7	3	
Decreased Appetite		5	4	
Musculoskeletal and Connective Tis	sue Disorders		•	
Musculoskeletal Stiffness		2	1	
Muscle Rigidity		2	1	
Nervous System Disorders			•	
Somnolence		16	4	
Headache		12	10	
Sedation		9	2	
Tremor		9	1	
Extrapyramidal Disorder		6	1	
Akathisia		6	4	
Drooling		3	0	
Lethargy		3	0	
Dizziness		3	2	
	·····×			
to your istry for to http:// istry/. ast milk. receive	ncluding hts. possible edicines	ion with iprazole ines you armacist	u to take f. soon as lose and	

What is the most important information I should know about aripiprazole oral solution?"

(For other side effects, also see "What are the possible side effects of aripiprazole oral solution?")

Serious side effects may happen when you take aripiprazole oral solution, including:

• Increased risk of death in elderly patients with dementia-related psychosis.

Medicines like aripiprazole oral solution can raise the risk of death in elderly people who have lost touch with reality (psychosis) due to confusion and memory loss (dementia). Aripiprazole oral solution 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:

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.

3. How can i watch for and try to prevent suicidal thoughts and actions in myself or 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 artidepressant 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. 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. Do not take aripiprazole oral solution if you are allergic to aripiprazole or any of the ingredients in aripiprazole oral solution. See the end of this Medication Guide for a complete list of ingredients in aripiprazole oral solution.

Before taking aripiprazole oral solution, 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 aripiprazole oral solution 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 aripiprazole oral solution will harm your unborn baby.

○ If you become pregnant while receiving aripiprazole oral solution, talk to your healthcare provider about register by calling 1-866-961-2388 orgo to http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/.

• breast-feeding or plans to breast-feed. Aripiprazole passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby if you receive aripiprazole oral solution. Tell your healthcare provider about all the medicines that you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Aripiprazole oral solution and other medicines may affect each other causing possible serious side effects. Aripiprazole oral solution may affect the way other medicines work, and other medicines may affect how aripiprazole oral solution works.

Your healthcare provider can tell you if it is safe to take aripiprazole oral solution with your other medicines. Do not start or stop any medicines while taking aripiprazole oral solution 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. ow should I take aripiprazole oral solution?

Take aripiprazole oral solution exactly as your healthcare provider tells you it. Do not change the dose or stop taking aripiprazole oral solution yourself. Aripiprazole oral solution can be taken with or without food.

If you miss a dose of aripiprazole oral solution, take the missed dose as soly you remember. If it is almost time for the next dose, just skip the missed do take your next dose at the regular time. Do not take two doses of aripiprazo disorder effective in ţ I talking (mania) Schizophrenia
 manic or mixed episodes that happen with bipo
 irritability associated with autistic disorder
 Tourette's disorder
 It is not known if aripiprazole oral solution is safe of 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 under 6 years of age with Tourette's disorder Aripiprazole oral solution?

Schizophrenia

manic or mixed episodes that happen with bigorintability associated with autistic disorder

Tourette's disorder MEDICATION G Aripiprazole Oral (AR i PIP ra z ng angry, or v mpulses n activity and t s in behavior o Call a healthcare provider right awatollowing symptoms, especially if the 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 acting on dangerous impulses an extreme increase in activity and other unusual changes in behavion

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	Percentage of Patients Reporting Reaction*			
System Organ Class	Aripiprazole Oral Solution	Placebo		
Preferred Term	(n=732)	(n=370)		
Dystonia	2	1		
Respiratory, Thoracic, and Mediastinal Disorders				
Epistaxis	2	1		
Skin and Subcutaneous Tissue Disorders				
Rash	2	1		
*Adverse reactions reported by at least 2% of pediatric pa which had an incidence equal to or less than placebo.	tients treated with oral aripipra.	zole, except adverse reactions		

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 aripiprazole to placebo. This analysis, stratified by study, indicated that the only adverse reaction to have a possible dose response relationship, and then most prominent only with 30 mg, was somnolence [including sedation]; (incidences were placebo, 7.1%; 10 mg, 8.5%; 15 mg, 8.7%; 20 mg, 7.5%; 30 mg, 12.6%).

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

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; fatique (incidences were placebo, 0%; 5 mg, 3.8%; 10 mg, 22.0%; 15 mg, 18.5%).

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

n short-term, placebo-controlled trials in schizophrenia in adults, the incidence of reported EPS-related events, excluding events related to akathisia, for aripiprazole-treated patients was 13% vs. 12% for placebo; and the incidence of akathisiarelated events for aripiprazole-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 aripiprazole-treated patients was 25% vs. 7% for placebo; and the incidence of akathisia-related events for aripiprazole-treated patients was 9% vs. 6% for placebo.

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

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

In the short-term, placebo-controlled trials in bipolar mania in adults, the incidence of reported EPS-related events, excluding events related to akathisia, for monotherapy aripiprazole-treated patients was 16% vs. 8% for placebo and the incidence of akathisia-related events for monotherapy aripiprazole-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 aripiprazole-treated patients was 15% vs. 8% for adjunctive placebo and the incidence of akathisia-related events for adjunctive aripiprazole-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 aripiprazole -treated patients was 26% vs. 5% for placebo and the incidence of akathisia-related events for aripiprazole-treated patients was 10% vs. 2% for placebo

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

Particle 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 aripiprazole-treated patients was 18% vs. 2% for placebo and the incidence of akathisia-related events for aripiprazole-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 aripiprazole and placebo (aripiprazole, 0.1; placebo, –0.4). Changes in the Barnes Akathisia Scale and the Assessments of Involuntary Movement Scales were similar for the aripiprazole and placebo groups.

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 aripiprazole-treated patients was 7% vs. 6% for placebo and the incidence of akathisia-related events for aripiprazole-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 aripiprazole and placebo.

inia, prolonged abnormal contractions of muscle gr lups, may occur in susceptible individ 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 aripiprazole and placebo in patients with schizophrenia were generally consistent with those reported in the short-term, placebo-controlled trials, except for a higher incidence of tremor [8% (12/153) for aripiprazole vs. 2% (3/153) for placebo]. In this study, the majority of the cases of tremor were of mild intensity (8/12 mild and 4/12 moderate), occurred early in therapy (9/12 ≤49 days), and were of limited duration (7/12 ≤10 days). Tremor infrequently led to discontinuation (<1%) of aripiprazole. In addition, in a long-term (52 week), active-controlled study, the incidence of tremor was 5% (40/859) for aripiprazole. A similar profile was observed in a long-term gould be a support to the content of the content 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 Aripiprazole
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 are those occurring in at least 1/100 patients; infrequent adverse reactions are those occurring in 1/100 to 1/1000 patients; rare

reactions are those occurring in fewer than 1/1000 patients: Adults - 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

infrequent - photophobia; rare - diplopia Gastrointestinal Disorders: *infrequent* - gastroesophageal reflux disease

Eye Disorders

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

Hepatobiliary Disorders Immune System Disorders

rare - hypersensitivity Injury, Poisoning, and Procedural Complications

frequent - blood prolactin decreased, 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

infrequent - parkinsonism, memory impairment, cogwheel rigidity, hypokinesia, bradykinesia; rare - akinesia, myoclonus, coordination abnormal, speech disorder, Grand Mal convulsion; <1/10,000 patients - choreoathetosis infrequent – aggression, loss of libido, delirium; rare – libido increased, anorgasmia, tic, homicidal ideation, catatonia,

Renal and Urinary Disorders

infrequent - erectile dysfunction; rare – gynaecomastia, menstruation irregular, amenorrhea, breast pain, priapism Respiratory, Thoracic, and Mediastinal Disorders:

infrequent - rash, hyperhidrosis, pruritus, photosensitivity reaction, alopecia; rare -urticaria Vascular Disorders. infrequent – hypotension, hypertension

sleep walking

<u>Pediatric Patients - Oral Administration</u>
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.

infrequent - oculogyric crisis

Gastrointestinal Disorders: infrequent -tonque dry, tonque spasm

Investigations: frequent - blood insulin increased Nervous System Disorders:

infrequent - sleep talking Renal and Urinary Disorders: Skin and Subcutaneous Tissue Disorders: infrequent - hirsutism

6.2 Postmarketing Experience The following adverse reactions have been identified during post-approval use of aripiprazole. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to establish a causal relationship to drug exposure: occurrences of allergic reaction (anaphylactic reaction, angioedema, laryngospasm, pruritus/urticaria, or oropharyngeal spasm), pathological gambling, hiccups, blood glucose fluctuation, oculogyric crisis, drug reaction with eosinophilia and systemic symptoms (DRESS) and fecal incontinence. 7 DRUG INTERACTIONS

7.1 Drugs Having Clinically Important Interactions with Aripiprazole

Concomitant Drug Name or Drug Class	Clinical Rationale	Clinical Recommendation
Strong CYP3A4 Inhibitors (e.g., itraconazole, clarithromycin) or strong CYP2D6 inhibitors (e.g., quinidine, fluoxetine, paroxetine)	The concomitant use of aripiprazole with strong CYP3A4 or CYP2D6 inhibitors increased the exposure of aripiprazole compared to the use of aripiprazole alone [see Clinical Pharmacology (12.3)].	With concomitant use of aripiprazole with a strong CYP3A4 inhibito or CYP2D6 inhibitor, reduce the aripiprazole dosage [see Dosage and Administration (2.7)].
Strong CYP3A4 Inducers (e.g., carbamazepine, rifampin)	The concomitant use of aripiprazole and carbamazepine decreased the exposure of aripiprazole compared to the use of aripiprazole alone [see Clinical Pharmacology (12.3)].	With concomitant use of aripiprazol with a strong CYP3A4 inducer, conside increasing the aripiprazole dosage [se Dosage and Administration (2.7)].
Antihypertensive Drugs	Due to its alpha adrenergic antagonism, aripiprazole has the potential to enhance the effect of certain antihypertensive agents.	Monitor blood pressure and adjust dose accordingly [see Warnings and Precautions (5.8)].
Benzodiazepines (e.g., lorazepam)	The intensity of sedation was greater with the combination of oral aripiprazole and lorazepam as compared to that observed with aripiprazole alone. The orthostatic hypotension observed was greater with the combination as compared to that observed with lorazepam alone [see	Monitor sedation and blood pressure. Adjust dose accordingly.

Warnings and Precautions (5.8)]. 7.2 Drugs Having No Clinically Important Interactions with Aripiprazole Based on pharmacokinetic studies, no dosage adjustment of aripiprazole is required when administered concomitantly with famotidine, valproate, lithium, lorazepam.

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

8.1 Pregnancy <u>Pregnancy Exposure Registry</u>
There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to atypical antipsychotics, including aripiprazole, during pregnancy. Healthcare providers are encouraged to register patients by contacting the National Pregnancy Registry for Atypical Antipsychotics at 1-866-961-2388 or visit http://womensmentalhealth.org/clinical-and-

Veonates exposed to antipsychotic drugs, including aripiprazole, during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery (see Clinical Considerations). Overall available data from published epidemiologic studies of pregnant women exposed to aripiprazole have not established a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes (see Data). There are risks to the mother associated with untreated schizophrenia, bipolar I disorder, or another indication, and with exposure to antipsychotics, including aripiprazole, during pregnancy (see Clinical Considerations). Aripiprazole exposure during pregnancy can have variable effects

on milk supply in the post-partum period. [see Use in Specific Populations (8.2)]. In animal reproduction studies, oral and intravenous aripiprazole administration during organogenesis in rats and/or rabbits at doses 10 and 19 times, respectively, the maximum recommended human dose (MRHD) of 30 mg/day based on mg/m² body surface area, produced fetal death, decreased fetal weight, undescended testicles, delayed skeletal ossification, skeletal abnormalities, and diaphragmatic hernia. Oral and intravenous aripiprazole administration during the pre- and post-natal period in rats at doses 10 times the MRHD based on mg/m² body surface area, produced prolonged gestation, stillbirths, decreased pup weight, and decreased pup survival (see Data).

The background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Disease-associated maternal and/or embryo/fetal risk The effects of aripiprazole on the exposures of other drugs are summarized in Figure 3. The effects of aripiprazole on the exposures of other drugs are summarized in Figure 3. including preterm birth. It is not known if this is a direct result of the illness or other comorbid factors.

Clinical Considerations

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 aripiprazole) during the third trimester of pregnancy. These symptoms have varied in severity. Monitor neonates for extrapyramidal and/or

withdrawal symptoms, and manage symptoms appropriately. Some neonates recovered within hours or days without specific

Published data from observational studies, birth registries, and case reports on the use of atypical antipsychotics during pregnancy do not report a clear association with antipsychotics and major birth defects. A retrospective study from a Medicaid database of 9258 women exposed to antipsychotics during pregnancy did not indicate an overall increased risk for major

Animal Data In animal studies, aripiprazole demonstrated developmental toxicity, including possible teratogenic effects in rats and rabbits. In pregnant rats treated orally with aripiprazole during organogenesis at doses of 3, 10, and 30 mg/kg/day, which are approximately 1, 3 and 10 times the MRHD of 30 mg/day based on mg/m² body surface area, a slight prolongation of gestation and delay in fetal development, as evidenced by decreased fetal weight and undescended testes, were observed at 10 times the MRHD. Delayed skeletal ossification was observed at 3 and 10 times the MRHD. Delayed skeletal ossification was observed at 3 and 10 times the MRHD. Delayed skeletal ossification was observed at 3 and 10 times the MRHD. Delayed skeletal ossification was observed at 3 and 10 times the MRHD. On the other dose groups were not examined for these findings). Postnatally, delayed vaginal opening was seen at 3 and 10 times the MRHD. Impaired oductive performance (decreased fertility rate, corpora lutea, implants, live fetuses, and increased post-implantation loss, y mediated through effects on female offspring) were observed at 10 times the MRHD; however, there was no evidence to suggest that these developmental effects were secondary to maternal toxicity. In pregnant rats injected intravenously with aripiprazole during organogenesis at doses of 3, 9, and 27 mg/kg/day, which are

1, 3, and 9 times the MRHD of 30 mg/day based on mg/m² body surface area, decreased fetal weight and delayed skeletal ossification were observed at 9 times the MRHD; this dose also caused maternal toxicity. In pregnant rabbits treated orally with aripiprazole during organogenesis at doses of 10, 30, and 100 mg/kg/day which are 6, 19, and 65 times the MRHD of 30 mg/day based on mg/m² body surface area, decreased maternal food consumption, and increased abortions as well as increased fetal mortality were observed at 65 times the MHRD. Decreased fetal weight and increased incidence of fused sternebrae were observed at 19 and 65 times the MRHD.

In pregnant rabbits injected intravenously with aripiprazole during organogenesis at doses of 3, 10, and 30 mg/kg/day, which are 2, 6, and 19 times the MRHD of 30 mg/day based on mg/m² body surface area, decreased fetal weight, increased fetal abnormalities (primarily skeletal), and decreased fetal skeletal ossification were observed at 19 times the MRHD; this dose also caused maternal toxicity. The fetal no-effect dose was 10 mg/kg/day, which is 6 times the MRHD. In rats treated orally with aripiprazole peri- and post-natally from gestation day 17 through postpartum day 21 at doses of 3, 10, and 30 mg/kg/day which are 1, 3, and 10 times the MRHD of 30 mg/day based on mg/m² body surface area slight maternal toxicity and slightly prolonged gestation were observed at 10 times the MHRD. An increase in stillbirths and, decreases in pup veight (persisting into adulthood) and survival were also seen at this dose.

In rats injected intravenously with aripiprazole from gestation day 6 through lactation day 20 at doses of 3, 8, and 20 mg/kg/day, which are 1, 3, and 6 times the MRHD of 30 mg/day based on mg/m² body surface area, increased stillbirths were observed at 3 and 6 times the MRHD; and decreases in early postnatal pup weight and survival were observed at 6 times the MRHD; these doses also caused some maternal toxicity. There were no effects on postnatal behavioral and reproductive 8.2 Lactation

Risk Summary

Aripiprazole is present in human breast milk. Based on published case reports and pharmacovigilance reports, aripiprazole exposure during pregnancy and/or the postpartum period can lead to variable effects on milk supply in the post-partum period, including clinically relevant decreases in milk supply which may be reversible with discontinuation of the drug. There are also reports of aripiprazole exposure during pregnancy and no maternal milk supply in the post-partum period. Effects on milk supply are likely mediated through decreases in prolactin levels, which have been observed [see Adverse Reactions (6.2)]. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for aripiprazole, and any potential adverse effects on the breastfed infant from ariniprazole, or from the underlying maternal condition Clinical Considerations

nitor infants exposed to aripiprazole through breastmilk for dehydration and lack of appropriate weight gain. The pharmacokinetics of aripiprazole and dehydro-aripiprazole in pediatric patients, 10 to 17 years of age, were similar to those in adults after correcting for the differences in body weight [see Clinical Pharmacology (12.3)]

Safety and effectiveness in pediatric patients with schizophrenia were established in a 6-week, placebo-controlled clinical trial in 202 pediatric patients aged 13 to 17 years [see Dosage and Administration (2.1), Adverse Reactions (6.1), and Clinical Studies (14.1)]. Although maintenance efficacy in pediatric patients has not been systematically evaluated, maintenance officacy can be extrapolated from adult data along with comparisons of aripiprazole pharmacokinetic parameters in adult and pediatric patients.

Safety and effectiveness in pediatric patients with bipolar mania were established in a 4-week, placebo-controlled clinical trial in 197 pediatric patients aged 10 to 17 years [see Dosage and Administration (2.2), Adverse Reactions (6.1), and Clinical Studies (14.2)]. Although maintenance efficacy in pediatric patients has not been systematically evaluated, maintenance efficacy can be extrapolated from adult data along with comparisons of aripiprazole pharmacokinetic parameters in adult

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

Safety and effectiveness in pediatric patients demonstrating irritability associated with autistic disorder were established in two 8-week, placebo-controlled clinical trials in 212 pediatric patients aged 6 to 17 years [see Indications and Usage (1), Dosage and Administration (2.4), Adverse Reactions (6.1), and Clinical Studies (14.4)]. A maintenance trial was conducted in pediatric patients (6 to 17 years of age) with irritability associated with autistic disorder. The first phase of this trial was an open-label, flexibly dosed (aripiprazole 2 to 15 mg/day) phase in which patients were stabilized (defined as > 25% improvement on the ABC-I subscale, and a CGI-I rating of "much improved" or "very much improved") on aripiprazole for 12 consecutive weeks. Overall, 85 patients were stabilized and entered the second, 16-week, double-blind phase where they were randomized to either continue aripiprazole treatment or switch to placebo. In this trial, the efficacy of

Safety and effectiveness of aripiprazole in pediatric patients with Tourette's Disorder were established in one 8-week (aged 7 to 17) and one 10-week trial (aged 6 to 18) in 194 pediatric patients [see Dosage and Administration (2.5), Adverse Reactions (6.1), and Clinical Studies (14.5)]. Maintenance efficacy in pediatric patients has not been systematically evaluated.

aripiprazole for the maintenance treatment of irritability associated with autistic disorder was not establi

Aripiprazole in juvenile rats caused mortality. CNS clinical signs, impaired memory and learning, and delayed sexual maturation when administered at oral doses of 10, 20, 40 mg/kg/day from weaning (21 days old) through maturity (80 days old). At 40 mg/kg/day, mortality, decreased activity, splayed hind limbs, hunched posture, ataxia, tremors and other CNS signs were observed in both genders. In addition, delayed sexual maturation was observed in males. At all doses and in a dose-dependen manner, impaired memory and learning, increased motor activity, and histopathology changes in the pituitary (atrophy), adrenals (adrenocortical hypertrophy), mammary glands (hyperplasia and increased secretion), and female reproductive organs (vaginal mucification, endometrial atrophy, decrease in ovarian corpora lutea) were observed. The changes in female oductive organs were considered secondary to the increase in prolactin serum levels. A No Observed Adverse Effect Level (MOAEL) could not be determined and, at the lowest tested dose of 10 mg/kg/day, there is no safety margin relative to the systemic exposures (AUCo = 24) for aripiprazole or its major active metabolite in adolescents at the maximum recommended

pediatric dose of 15 mg/day. All drug-related effects were reversible after a 2-month recovery period, and most of the drug Aripiprazole in juvenile dogs (2 months old) caused CNS clinical signs of tremors, hypoactivity, ataxia, recumbency and limited use of hind limbs when administered orally for 6 months at 3, 10, 30 mg/kg/day. Mean body weight and weight gain were decreased up to 18% in females in all drug groups relative to control values. A NOAEL could not be determined and, at the lowest tested dose of 3 mg/kg/day, there is no safety margin relative to the systemic exposures (AUC0 m24) for aripiprazole or its major active metabolite in adolescents at the maximum recommended pediatric dose of 15 mg/day. All drug-related effects were reversible after a 2-month recovery period.

8.5 Geriatric Use Vo dosage adjustment is recommended for elderly patients [see Boxed Warning, Warnings and Precautions (5.1), and Clinical Pharmacology (12.3)]. Of the 13,543 patients treated with oral aripiprazole in clinical trials, 1073 (8%) were ≥65 years old and 799 (6%) were ≥75 years old. Placebo-controlled studies of oral aripiprazole in schizophrenia, bipolar mania, or another indication did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Aripiprazole is not approved for the treatment of patients with psychosis associated with Alzheimer's disease [see Boxed

Dosage adjustment is recommended in known CYP2D6 poor metabolizers due to high aripiprazole concentrations. Approximately 8% of Caucasians and 3 to 8% of Black/African Americans cannot metabolize CYP2D6 substrates and are classified as poor metabolizers (PM) [see Dosage and Administration (2.7) and Clinical Pharmacology (12.3)].

No dosage adjustment for aripiprazole 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)].

No dosage adjustment for aripiprazole is required on the basis of a patient's sex, race, or smoking status [see Clinical Pharmacology (12.3)1.

9 DRUG ARUSE AND DEPENDENCE 9.1 Controlled Substance Aripiprazole is not a controlled substance

8.6 CYP2D6 Poor Metabolizers

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

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,

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

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

10.2 Management of Overdosage

No specific information is available on the treatment of overdose with aripiprazole. An electrocardiogram should be obtained in case of overdosage and if OT 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 aripiprazole, an early charcoal administration may be useful in partially preventing the absorption of aripiprazole. Administration of 50 g of activated charcoal, one hour after a single 15 mg oral dose of aripiprazole, decreased the mean AUC and C_{max} of aripiprazole by 50%. Hemodialysis: Although there is no information on the effect of hemodialysis in treating an overdose with aripiprazole hemodialysis is unlikely to be useful in overdose management since aripiprazole is highly bound to plasma proteins.

Aripiprazole is an atypical antipsychotic drug that is available as aripiprazole oral solution. Aripiprazole is 7-[4-[4-(2,3-Dichlorophenyl) piperazin-1-yl] butoxy]-3, 4-dihydroquinolin-2(1*H*)-one. The molecular formula is C₂₃H₂₇Cl₂N₃O₂, and molecular weight is 448.39. The chemical structure is as follows:

Aripiprazole 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 edetate disodium, fructose, glycerin, malic acid, methylparaben, propylene glycol, propylparaben, purified water, sodium hydroxide, sucrose. The oral solution is orange flavored. 12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action The mechanism of action of aripiprazole in schizophrenia or bipolar mania, is unclear. However, the efficacy of aripiprazole in the listed indications could be mediated through a combination of partial agonist activity at D_2 and $S-HT_{DA}$ receptors and antagonist activity at $S-HT_{DA}$ receptors. 12.2 Pharmacodynamics

Aripiprazole exhibits high affinity for dopamine D₂ and D₃, serotonin 5-HT_{1A} and 5-HT_{2A} receptors (K₁ values of 0.34 nM, 0.8 nM, 1.7 nM, and 3.4 nM, respectively), moderate affinity for dopamine D₄, serotonin 5-HT_{2C} and 5-HT₇, alpha--adrenergic and histamine H₁ receptors (K₁ values of 44 nM, 15 nM, 39 nM, 57 nM, and 61 nM, respectively), and moderate affinity for the serotonin reuptake site (K≔98 nM). Aripiprazole has no appreciable affinity for cholinergic muscarinic receptors (IC₅o>1000

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 D₂ 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 sozymes, CYP2D6 and CYP3A4. For CYP2D6 poor metabolizers, the mean elimination half-life for aripiprazole is about 146

ORAL ADMINISTRATION

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 C_{max} 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. 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 Metabolism and Elimination 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.

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. 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 C_{max} 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 C_{max} and AUC values at steady-state is expected in poor metabolizers of CYP2D6 administered with strong CYP3A4 inhibitors.

Following a single oral dose of [14C]-labeled aripiprazole, approximately 25% and 55% of the administered radioactivity

Figure 1: The effects of other drugs on aripiprazole pharmacokinetics Effect of Other Drugs on Ari

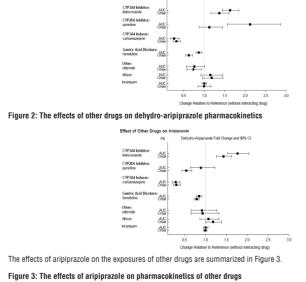
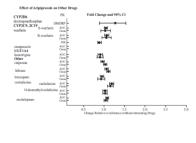
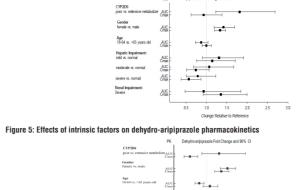


Figure 3: The effects of aripiprazole on pharmacokinetics of other drugs



Studies in Specific Populations Exposures of aripiprazole and dehydro-aripiprazole in specific populations are summarized in Figure 4 and Figure 5, respectively. In addition, in pediatric patients (10 to 17 years of age) administered with aripiprazole (20 mg to 30 mg), the body weight corrected aripiprazole clearance was similar to the adults Figure 4: Effects of intrinsic factors on aripiprazole pharmacokinetics



13 NONCLINICAL TOXICOLOGY 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Lifetime carcinogenicity studies were conducted in ICR mice, F344 rats, and Sprague-Dawley (SD) 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, 0.5, 2 and 5 times and 0.3, 1 and 3 times the MRHD of 30 mg/day based on mg/m² body surface area, respectively). In addition, SD rats were dosed orally for 2 years at 10, 20, 40, and 60 mg/kg/day, which are 3, 6, 13 and 19 times the MRHD based on mg/m² body surface area. 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 adenocarchomas were increased at dietary doses of 3 to 30 mg/kg/day (0.5 to 5 times the MRHD). In female rats, the incidence of mammary gland fibroadenomas was increased at a dietary dose of 10 mg/kg/day (3 times the MRHD); and the incidences of adrenocortical carcinomas and combined adrenocortical adenomas/carcinomas were increased at an oral dose of 60 mg/kg/day (19 times the MRHD). An increase in mammary, pituitary, and endocrine pancreas neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be mediated by prolonged dopamine D2-receptor antagonism and hyperprolactinemia. 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

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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* ohromosomal aberration assay in chinese hamster lung (CHL) cells, the *in vivo* micronucleus assay in mice, and the unscheduled DNA synthesis assay in rats. Aripiprazole and a metabolite (2,3-DCPP) were clastogenic in the *in vitro* chromosomal aberration assay in CHL cells with and without metabolic activation. The metabolite, 2,3-DCPP, increased 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.

male rats were treated orally with aripiprazole from 2 weeks prior to mating through gestation day 7 at doses of 2, 6, and 20 mg/kg/day, which are 0.6, 2, and 6 times the MRHD of 30 mg/day based on mg/m² body surface area. 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 2 and 6 times the MRHD, and decreased fetal weight was seen at 6 times the MRHD. Male rats were treated orally with aripiprazole from 9 weeks prior to mating through mating at doses of 20, 40, and 60 mg/kg/day, which are 6, 13, and 19 times the MRHD of 30 mg/day based on mg/m² body surface area. Disturbances in spermatogenesis were seen at 19 times the MRHD and prostate atrophy was seen at 13 and 19 times the MRHD without impairment of fertility.

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/day and in a 2-year carcinogenicity study at doses of 40 and 60 mg/kg/day which are 13 and 19 times the MRHD of 30 mg/day based on mg/m² body surface area. 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 ficacy of the oral formulations of aripiprazole was established in the following adequate and well-controlled trials Four short-term trials and one maintenance trial in adult patients and one short-term trial in adolescents (ages 13 to 17)

with schizophrenia [see Clinical Studies (14.1)]
Four short-term monotherapy trials and one 6-week adjunctive trial in adult patients and one short-term monotherapy trial in pediatric patients (ages 10 to 17) with manic or mixed episodes [see Clinical Studies (14.2)] One maintenance monotherapy trial and in one maintenance adjunctive trial in adult patients with bipolar I disorder [see Two short-term trials in pediatric patients (ages 6 to 17 years) for the treatment of irritability associated with autistic

disorder [see Clinical Studies (14.4)] Two short-term trials in pediatric patients (ages 6 to 18 years) with Tourette's disorder [see Clinical Studies (14.5)]

The efficacy of aripiprazole in the treatment of schizophrenia was evaluated in five short-term (4-week and 6-week), placebo-

controlled trials of acutely relapsed inpatients who predominantly met DSM-III/IV criteria for schizophrenia. Four of the five trials were able to distinguish aripiprazole from placebo, but one study, the smallest, did not. Three of these studies also included an active control group consisting of either risperidone (one trial) or haloperidol (two trials), but they were not designed to allow for a comparison of aripiprazole and the active comparators. In the four positive trials for aripiprazole, four primary measures were used for assessing psychiatric signs and symptoms Efficacy was evaluated using the total score on the Positive and Negative Syndrome Scale (PANSS). The PANSS is a 30 item scale that measures positive symptoms of schizophrenia (7 items), negative symptoms of schizophrenia (7 items), and general psychopathology (16 items), each rated on a scale of 1 (absent) to 7 (extreme); total PANSS scores range from 30 to 210. The Clinical Global Impression (GGI) assessment reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient.

In a 4-week trial (n=414) comparing two fixed doses of aripiprazole (15 or 30 mg/day) to placebo, both doses of aripiprazole were superior to placebo in the PANSS total score (Study 1 in Table 26), PANSS positive subscale, and CGI-severity score. In addition, the 15 mg dose was superior to placebo in the PANSS negative subscale. In a 4-week trial (n=404) comparing two fixed doses of aripiprazole (20 or 30 mg/day) to placebo, both doses of aripiprazole were superior to placebo in the PANSS total score (Study 2 in Table 26), PANSS positive subscale, PANSS negative subscale, and CGI-severity score.

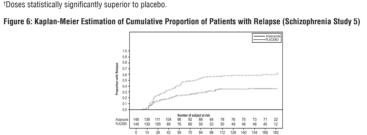
In a 6-week trial (n=420) comparing three fixed doses of aripiprazole (10, 15, or 20 mg/day) to placebo, all three doses of aripiprazole were superior to placebo in the PANSS total score (Study 3 in Table 26), PANSS positive subscale, and the PANSS In a 6-week trial (n=367) comparing three fixed doses of aripiprazole (2, 5, or 10 mg/day) to placebo, the 10 mg dose of aripiprazole was superior to placebo in the PANSS total score (Study 4 in Table 26), the primary outcome measure of the study. The 2 and 5 mg doses did not demonstrate superiority to placebo on the primary outcome measure. hus, the efficacy of 10, 15, 20, and 30 mg daily doses was established in two studies for each dose. Among these doses,

there was no evidence that the higher dose groups offered any advantage over the lowest dose group of these studies An examination of population subgroups did not reveal any clear evidence of differential responsiveness on the basis of age, A longer-term trial enrolled 310 inpatients or outpatients meeting DSM-IV criteria for schizophrenia who were, by history symptomatically stable on other antipsychotic medications for periods of 3 months or longer. These patients were discontinued from their antipsychotic medications for periods of 3 months or longer. These patients were discontinued from their antipsychotic medications and randomized to aripiprazole 15 mg/day or placebo for up to 26 weeks of observation for relapse. Relapse during the double-blind phase was defined as CGI-Improvement score of ≥5 (minimally worse), scores ≥5 (moderately severe) on the hostility or uncooperativeness items of the PANSS, or ≥20% increase in the PANSS total score. Patients receiving aripiprazole 15 mg/day experienced a significantly longer time to relapse over the subsequent 26 weeks compared to those receiving placebo (Study 5 in Figure 6).

The efficacy of aripiprazole in the treatment of schizophrenia in pediatric patients (13 to 17 years of age) was evaluated in one 6-week, placebo-controlled trial of outpatients who met DSM-IV criteria for schizophrenia and had a PANSS score ≥70 at baseline. In this trial (n=302) comparing two fixed doses of aripiprazole (10 or 30 mg/day) to placebo, aripiprazole was titrated starting from 2 mg/day to the target dose in 5 days in the 10 mg/day treatment arm. Both doses of aripiprazole were superior to placebo in the PANSS total score (Study 6 in Table 26), the primary outcome measure of the study. The 30 mg/day dosage was not shown to be more efficacious than the 10 mg/day dose. Although maintenance efficacy in pediatric patients has not been systematically evaluated, maintenance efficacy can be extrapolated from adult data along with comparisons of aripiprazole pharmacokinetic parameters in adult and pediatric patients.

		Primary Efficacy Measure: PANSS			
Study Number	Treatment Group	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference* (95% CI)	
Study 1	Aripiprazole Oral Solution (15 mg/day) †	98.5 (17.2)	-15.5 (2.40)	-12.6 (-18.9, -6.2)	
	Aripiprazole Oral Solution (30 mg/day)†	99 (19.2)	-11.4 (2.39)	-8.5 (-14.8, -2.1)	
	Placebo	100.2 (16.5)	-2.9 (2.36)		
Study 2	Aripiprazole Oral Solution (20 mg/day)†	92.6 (19.5)	-14.5 (2.23)	-9.6 (-15.4, -3.8)	
	Aripiprazole Oral Solution (30 mg/day)†	94.2 (18.5)	-13.9 (2.24)	-9.0 (-14.8, -3.1)	
	Placebo	94.3 (18.5)	-5.0 (2.17)		
Study 3	Aripiprazole Oral Solution (10 mg/day)†	92.7(19.5)	-15.0 (2.38)	-12.7 (-19, -6.41)	
	Aripiprazole Oral Solution (15 mg/day)†	93.2 (21.6)	-11.7 (2.38)	-9.4 (-15.71, -3.08)	
	Aripiprazole Oral Solution (20 mg/day)†	92.5 (20.9)	-14.4 (2.45)	-12.1 (-18.53, -5.68	
	Placebo	92.3 (21.8)	-2.3 (2.35)		
Study 4	Aripiprazole Oral Solution (2 mg/day)	90.7(14.5)	-8.2 (1.90)	-2.9 (-8.29, 2.47)	
	Aripiprazole Oral Solution (5 mg/day)	92.0 (12.6)	-10.6 (1.93)	-5.2 (-10.7, 0.19)	
	Aripiprazole Oral Solution (10 mg/day)†	90.0 (11.9)	-11.3 (1.88)	-5.9 (-11.3, -0.58)	
	Placebo	90.8 (13.3)	-5.3 (1.97)		
Study 6	Aripiprazole Oral Solution (10 mg/day)†	93.6 (15.7)	-26.7 (1.91)	-5.5 (-10.7, -0.21)	
(Pediatric, 13 to 17 years)	Aripiprazole Oral Solution (30 mg/day)†	94.0 (16.1)	-28.6 (1.92)	-7.4 (-12.7, -2.13)	
10 to 17 years)	Placebo	94.6 (15.6)	-21.2 (1.93)		

Difference (drug minus placebo) in least-squares mean change from baseline Doses statistically significantly superior to placebo



14.2 Bipolar DisorderAcute Treatment of Manic and Mixed Episodes

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

without a rapid-cycling course. The primary instrument used for assessing manic symptoms was the Young Mania Rating Scale (Y-MRS), an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology in a range from 0 (no manic features) to 60 (maximum score). A key secondary instrument included the Clinical Global Impression-Bipolar (CGI-BP) Scale. In the four positive, 3-week, placebo-controlled trials (n=268; n=248; n=480; n=485) which evaluated aripiprazole in a range of 15 mg to 30 mg, once daily (with a starting dose of 30 mg/day in two studies and 15 mg/day in two studies), aripiprazole was superior to placebo in the reduction of Y-MRS total score (Studies 1 to 4 in Table 27) and CGI-BP Severity of Illness score (mania). In the two studies with a starting dose of 15 mg/day, 48% and 44% of patients were on 15 mg/day at endpoint. In the two studies with a starting dose of 30 mg/day, 86% and 85% of patients were on 30 mg/day at endpoin

The efficacy of adjunctive aripiprazole with concomitant lithium or valproate in the treatment of manic or mixed episodes was established in a 6-week, placebo-controlled study (n=384) with a 2-week lead-in mood stabilizer monotherapy phase in adult atients 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 mEg/L) or valproate (50 to 125 µg/mL) at therapeutic serum levels

and remained on stable doses for 2 weeks. At the end of 2 weeks, patients demonstrating inadequate response (Y-MRS total score ≥16 and ≤25% improvement on the Y-MRS total score) to lithium or valproate were randomized to receive either aripiprazole (15 mg/day or an increase to 30 mg/day as early as day 7) or placebo as adjunctive therapy with open-label lithium or valproate. In the 6-week, placebo-controlled phase, adjunctive aripiprazole 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. The efficacy of aripiprazole 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 aripiprazole (10 or 30 mg/day) to placebo. The aripiprazole 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 aripiprazole were superior to placebo in change from baseline to week 4 on the Y-MRS total score (Study 6 in Table 27). Primary Efficacy Measure: Y-MRS

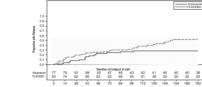
Number	Treatment Group	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference* (95% CI)
Study 1	Aripiprazole Oral Solution (30 / 15 mg/day) †	29.0 (5.9)	-12.52 (1.05)	-5.33 (-7.90, -2.76)
	Placebo	28.5 (4.6)	-7.19 (1.07)	
Study 2	Aripiprazole Oral Solution (30 / 15 mg/day) †	27.8 (5.7)	-8.15 (1.23)	-4.80 (-7.80, -1.80)
	Placebo	29.1 (6.9)	-3.35 (1.22)	
Study 3	Aripiprazole Oral Solution (15 to 30 mg/day) †	28.5 (5.6)	-12.64 (0.84)	-3.63 (-5.75, -1.51)
	Placebo	28.9 (5.9)	9.01 (0.81)	
Study 4	Aripiprazole Oral Solution (15 to 30 mg/day) †	28.0 (5.8)	-11.98 (0.80)	-2.28 (-4.44, -0.11)
	Placebo	28.3 (5.8)	-9.70 (0.83)	
Study 5	Aripiprazole Oral Solution (15 or 30 mg/day)† +Lithium/Valproate	23.2 (5.7)	-13.31 (0.50)	-2.62 (-4.29, -0.95)
	Placebo +Lithium/Valproate	23.0 (4.9)	-10.70 (0.69)	
Study 6	Aripiprazole Oral Solution (10 mg/day)†	29.8 (6.5)	-14.2 (0.89)	-5.99 (-8.49, -3.50)
(Pediatric, 10 to 17 years)	Aripiprazole Oral Solution (30 mg/day)†	29.5 (6.3)	-16.5 (0.87)	-8.26 (-10.7, -5.77)
10 to 17 years)	Placebo	30.7 (6.8)	-8.2 (0.91)	

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

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 aripiprazole and who had maintained a clinical response for at least 6

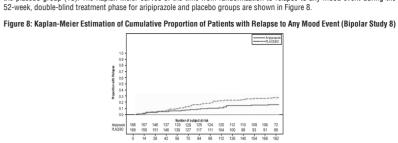
weeks. The first phase of this trial was an open-label stabilization period in which inpatients and outpatients were clinically stabilized and then maintained on open-label aripiprazole (15 or 30 mg/day, with a starting dose of 30 mg/day) for at least 6 consecutive weeks. One hundred sixty-one outpatients were then randomized in a double-blind fashion, to either the same dose of ariginarzole 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, aripiprazole 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 aripiprazole group and 36 were from the placebo group. The number of observed manic episodes in the aripiprazole group (6) were fewer than that in the placebo group (19), while the number of depressive episodes in the aripiprazole 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

Figure 7: Kaplan-Meier Estimation of Cumulative Proportion of Patients with Relanse (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 µg/mL) at therapeutic serum levels, and remained on stable doses for 2 weeks. At the end of 2 weeks, patients demonstrating inadequate response (Y-MRS total score ≥16 and ≤35% improvement on the Y-MRS total score) to lithium or valproate received aripiprazole 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 aripiprazole 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 aripiprazole they were on at the end of the stabilization period or placebo plus lithium or valproate and were thei monitored for manic, mixed, or depressive relapse for a maximum of 52 weeks. Aripiprazole 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 aripiprazole group and 43 were from the placebo group. The number of observed manic episodes in the aripiprazole group (7) were fewer than that in the placebo group (19), while the number of depressive episodes in the aripiprazole 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



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

14.4 Irritability Associated with Autistic Disorder Pediatric Patients The efficacy of 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-1V criteria for autistic disorder and demonstrated behaviors such as tantrums, aggression, self-injurious behavior, or a combination of these problems. Over 75% of these subjects were under 13 years of age.

Efficacy was evaluated using two assessment scales: the Aberrant Behavior Checklist (ABC) and the Clinical Global Impression-Improvement (CGI-I) scale. The primary outcome measure in both trials was the change from baseline to endpoint in the Irritability subscale of the ABC (ABC-I). The ABC-I subscale measured symptoms of irritability in autistic disorder. The results of these trials are as follows: In one of the 8-week, placebo-controlled trials, children and adolescents with autistic disorder (n=98), aged 6 to 17 years, received daily doses of placebo or aripiprazole 2 to 15 mg/day, aripiprazole, starting at 2 mg/day with increases allowed up to 15 mg/day based on clinical response, significantly improved scores on the ABC-I subscale and on the CGI-I scale compared with placebo. The mean daily dose of aripiprazole 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 aripiprazole (5 mg/day, 10 mg/day, or 15 mg/day) were compared to placebo. Aripiprazole dosing started at 2 mg/day and was increased to 5 mg/day after one week. After a second week, it was increased to 10 mg/day for patients in the 10 mg and 15 mg dose arms, and after a third week, it was increased to 15 mg/day in the 15 mg/day treatment arm (Study 2 in Table 29). All three doses of aripiprazole significantly improved scores on the ABC-I subscale compared with placebo Table 29: Irritability Associated with Autistic Disorder Studies (Pediatric) Primary Efficacy Measure: ARC-I

luuy Nullibei	rimary Lineacy Measure.			uic. ADO-i
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference* (95% CI)
Study 1	Aripiprazole Oral Solution (2 to 15 mg/day)†	29.6 (6.37)	-12.9 (1.44)	-7.9 (-11.7, -4.1)
	Placebo	30.2 (6.52)	-5.0 (1.43)	
	Aripiprazole Oral Solution (5 mg/day)†	28.6 (7.56)	-12.4 (1.36)	-4.0 (-7.7, -0.4)
Study 2	Aripiprazole Oral Solution (10 mg/day)†	28.2 (7.36)	-13.2 (1.25)	-4.8 (-8.4, -1.3)
	Aripiprazole Oral Solution (15 mg/day)†	28.9 (6.41)	-14.4 (1.31)	-6.0 (-9.6, -2.3)
	Placebo	28.0 (6.89)	-8.4 (1.39)	

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

† Doses statistically significantly superior to placebo

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

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

The results of these trials are as follows In the 8-week, placebo-controlled, fixed-dose trial, children and adolescents with Tourette's disorder (n=133), aged 7 to 17 years, were randomized 1:1:1 to low dose aripiprazole, high dose aripiprazole, or placebo. The target doses for the low and high dose aripiprazole groups were based on weight. Patients < 50 kg in the low dose aripiprazole 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 aripiprazole group, started at 2 mg per day increased to 5 mg per day after 2 days, with a subsequent increase to a target dose of 10 mg per day at day 7. Patient: 450 kg in the high dose aripiprazole group started at 2 mg per day increased to 5 mg per day after 2 days, with a subsequent increase to a target dose of 10 mg per day at day 7. Patients ≥ 50 kg in the high dose aripiprazole group, started at 2 mg per day increased to 5 mg per day after 2 days, with a subsequent increase to a dose of 10 mg per day after 2 days, with a subsequent increase to a dose of 10 mg per day after 2 days, with a subsequent increase to a dose of 10 mg per day at day 7 and were allowed weekly increases of 5 mg per day up to a target dose 20 mg per day at Day 21. Aripiprazole (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

Figure 9: Least Square Means of Change from Baseline in YGTSS TTS by Week (Tourette's Disorder Study 1) CHANGE IN YGTSS TOTAL TIC SCORE FROM BASELINE



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 aripiprazole, starting at 2 mg/day with increases allowed up to 20 mg/ day based on clinical response. Aripiprazole demonstrated statistically significantly improved scores on the YGTSS TTS scale compared with placebo (Study 2 in Table 30). The mean daily dose of aripiprazole at the end of 10-week treatment was 6.54

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

16 HOW SUPPLIED/STORAGE AND HANDLING 16.1 How Supplied Aripiprazole Oral Solution (1 mg/mL) is supplied in child-resistant bottles along with a calibrated oral dosing cup. Aripiprazole Oral Solution is available as follows: 150 mL Bottle

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 aripiprazole 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. 17 PATIENT COUNSELING INFORMATION Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Discuss the following issues with patients prescribed aripiprazole oral solution: 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 aripiprazole oral solution 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 aripiprazole oral solution. 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 aripiprazole oral solution is not approved as a single agent for treatment of depression and has not been evaluated in pediatric major depressive disorder.

Advise 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 oral solution. 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)]. Interference with Cognitive and Motor Performance
Because aripiprazole oral solution may have the potential to impair judgment, thinking, or motor skills, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that aripiprazole therapy does not affect them adversely [see Warnings and Precautions (5.12)].

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 aripiprazole oral solution contains 400 mg of sucrose and 200 mg of fructose.

Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during treatment with aripiprazole. Advise patients that aripiprazole may cause extrapyramidal and/or withdrawal symptoms (agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder) in a neonate. Advise patients that there is a pregnancy registry that monitors pregnancy outcomes in women exposed to aripiprazole during pregnancy [see Use in

Aripiprazole use during pregnancy may affect milk supply. Advise the lactating patient to discuss any plans for breastfeeding with their healthcare provider, and to monitor the breastfed infant for dehydration and lack of appropriate weight gain [see Use in Specific Populations (8.2)].

Inc. Piscataway, NJ 08854

Bv: HETERO™ Hetero Labs Limited Jeedimetla, Hyderabad - 500 055, India Revised: 10/2024

what are the possible side effects of aripiprazole oral solution?

What are the possible side effects of aripiprazole oral solution?

Aripiprazole oral solution may cause serious site effects, including:

See "What is the most important information I should know about aripiprazole oral solution?"

Stroke in edietrly people (cerebrovascular problems) that can lead to death. Call your healthcare provider right away if you have some or all of the following symptoms. high fivers. These may be symptoms of a rare and senious condition that can lead to death. Call your healthcare provider right away if you have any of these symptoms.

Incontrolled body movements (tartifue dystinesis), Aripiprazole oral solution may cause movements that you cannot control in your face, tongue, or other body parts, tardive dystinesia may also start after you stop receiving aripiprazole oral solution. Problems with your metabolism such as:

Incontrolled body movements (tartifue dystinesis), Aripiprazole oral solution. Problems with your metabolism such as:

Incontrolled body movements (tartifue dystinesis) and diabetes. Increases in blood sugar can head to coma or death. If you have diabetes or risk factors for idabetes (such as being overweight or a family history of diabetes), your healthcare provider should check your blood sugar before you start aripiprazole oral solution and during your treatment.

Call your healthcare provider should check your before you start aripiprazole oral solution. Provider while receiving aripiprazole oral solution:

Pele very finisty

Pele very finisty

Pele very finisty

Pele very finisty

Pele very may finish more than usual

Pele very may.

Pele very may finish more than usual

Pele very hungy.

Pele very may finish more than usual

Pele very hungs. Some people taking aripiprazole or solution have had unusual urges. Some people taking aripiprazole or solution rave had not sexual urges.

Problems with oral ramily members notice that you are having unusual urges or behaviors; all to your healthcare provid How should I store aripiprazole oral solution?
 Store aripiprazole oral solution at room temperature, between 68° to 77°F (20° to 2° Aripiprazole oral solution (1 mg/mL) is supplied in child-resistant bottles with a calibrated oral dosing cup.
 Opened bottles of aripiprazole oral solution can be used for up to 6 months opening, but not beyond the expiration date on the bottle.
 Keep aripiprazole oral solution and all medicines out of the reach of children General information about the safe and effective use of aripiprazole oral solution for a condition for what mas not prescribed. Do not use aripiprazole oral solution to other people, even in have the same symptoms you have. It may harm them. You can ask your healt provider or pharmacist for information about aripiprazole oral solution that was we for healthcare professionals. What are the ingredients in all Active ingredient: aripiprazole Inactive ingredients: edetate of propylene glycol, propylparabe solution is orange flavored. AMBER PHARMACEUTICALS, INC. s Medication G /ised: 10/2024 your doctor for medical at 1-800-FDA-1088. st common side effects of aripip
feeling sleepy
headache
vomiting
fatigue
increased or decreased appetite
uncontrolled movement such as
restlessness, tremor
are not all the possible side effects e information, ion Guide avail e taking aripiprazole oral so heavy machinery, or do othe e oral solution affects you. in aripi zole US ate diso raben, ripiprazole oral solution, call 1-800-222-1222 right away, e in a cool place if _l ot wear too much c piprazole (JSP sodium, fru , purified v -495-1995. effects of ari aripiprazole as as by effects. f possible. or heavy U.S I **solution?** her dangerous : u. Aripiprazole Food your or go oral solution Ξ. health to the report side Drug 9 Ind of children. vities until I solution I months (20° to bottles ral solution
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