

#### ARIPIPRAZOLE- oral solutio Quagen Pharmaceuticals LLC

# 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 SUICID 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 psychists. (3.1)
  Increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants. Monitor for worsening and emergence of suicidal thoughts and behaviors. (5.3)
- --- 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)
- Adjunctive Treatment of Major Depressive Disorder (14.3)
   Irritability Associated with Autistic Disorder (14.4) Treatment of Tourette's disorder (14.5)

# - DOSAGE AND ADMINISTRATION

Initial Dose Recommended Dose I				
Schizophrenia - adults (2.1)		10 to 15 mg/day	10 to 15 mg/day	30 mg/day
Schizophrenia - adolescents (2.1)		2 mg/day	10 mg/day	30 mg/day
Bipolar mania - adults: monotherapy (2.2)		15 mg/day	15 mg/day	30 mg/day
Bipolar mania - adults: adjunct to lithium or valproate (2.2)		10 to 15 mg/day	15 mg/day	30 mg/day
Bipolar mania - pediatric patients: monotherapy or as an adjunct to lithium or valproate (2.2)		2 mg/day	10 mg/day	30 mg/day
Major Depressive Disorder - Adults adjunct to antidepressants (2.3)		2 to 5 mg/day	5 to 10 mg/day	15 mg/day
Irritability associated with autistic disorder - pediatric patients (2.4)		2 mg/day	5 to 10 mg/day	15 mg/day
Touratta's disorder (2.5)	Patients < 50 kg	2 mg/day	5 mg/day	10 mg/day
Tourette's disorder – (2.5) Patients ≥ 50 kg		2 mg/day	10 mg/day	20 mg/day
<ul> <li>Oral formulations: Administer once daily without regard to meals (2)</li> <li>Known CYP2D6 poor metabolizers: Half of the usual dose (2.7)</li> </ul>				

- DOSAGE FORMS AND STRENGTHS - Oral Solution: 1 mg/mL (3) -- CONTRAINDICATIONS
- . Known hypersensitivity to aripiprazole (4) ---- WARNINGS AND PRECAUTIONS -
- Cerebrovascular Adverse Reactions in Elderly Patients with Dementia-Related Psychosis: Increased incidence of cerebrovascular adverse reactions (e.g., stroke, transient ischemic attack, including tatalities) (5.2)

  See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

# FULL PRESCRIBING INFORMATION: CONTENTS\*

#### WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS; AND SUICIDAL THOUGHTS AND BEHAVIORS WITH ANTIDEPRESSANT DRUGS I INDICATIONS AND USAGE 2 DOSAGE AND ADMINISTRATION

- 2.2 Bipolar I Disorder 2.3 Adjunctive Treatment of Major Depressive Disorder
- 2.3 Agriated Authorition and Authorition Disorder
  2.5 Tourette's Disorder
  2.7 Dosage Adjustments for Cytochrome P450 Considerations
- 2.8 Dosing of Oral Solution 3 DOSAGE FORMS AND STRENGTHS

# 4 CONTRAINDICATIONS 5 WARNINGS AND PRECAUTIONS

- i.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis 5.2 Cerebrovascular Adverse Events, Including Stroke
  5.3 Suicidal Thoughts and Behaviors in Children, Adolescents, and Young Adults
  5.4 Neuroleptic Malignant Syndrome (NMS)
- 5.5 Tardive Dyskinesia 5.6 Metabolic Changes 5.7 Pathological Gambling and Other Compulsive Behaviors
  5.8 Orthostatic Hypotension
- 5.10 Leukopenia, Neutropenia, and Agranulocytosis
- .11 Seizures/Convulsions .12 Potential for Cognitive and Motor Impairment 5.13 Body Temperature Regulation
- 6 ADVERSE REACTIONS
- 6.1 Clinical Trials Experience
- 7 DRUG INTERACTIONS
- 7.1 Drugs Having Clinically Important Interactions with aripiprazole 7.2 Drugs Having No Clinically Important Interactions with aripiprazole

# FULL PRESCRIBING INFORMATION

# WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS; AND SUICIDAL THOUGHTS AND Elderly patients with dementia-related psychosis treated with sychotic drugs are at an increased risk of death. Aripiprazole is approved for the treatment of patients with dementia-related hosis [see Warnings and Precautions (5.1)].

Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term studies. These studies did not show an increase in the risk of suicidal thoughts and behavior with 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 with the prescriber [see Warnings and Precautions (5.3)].

1 INDICATIONS AND USAGE Aripiprazole Oral Solution is indicated for the treatment of:

Schizophrenia Isee Clinical Studies (14.1)1

- Acute Treatment of Manic and Mixed Episodes associated with Bipolar I
- Irritability Associated with Autistic Disorder [see Clinical Studies (14.4)] Treatment of Tourette's Disorder [see Clinical Studies (14.5)]

## 2 DOSAGE AND ADMINISTRATION 2.1 Schizophrenia

The recommended starting and target dose for aripiprazole oral solution 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 [see Clinical

Maintenance Treatment: Maintenance of efficacy in schizophrenia was Mallituation: Heathfeith maintenance of emissay in Society and demonstrated in a trial involving patients with schizophrenia who had been symptomatically stable on other antipsychotic medications for periods of 3 months or longer. These patients were discontinued from those medications and randomized to either aripiprazole oral solution 15 mg/day or placebo, and

observed for relanse Isee Clinical Studies (14.1)1. Patients should be periodical The recommended target dose of aripiprazole oral solution 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 act showed to be opposed frequently and 10 mg/day 10 mg/day.

dose was not shown to be more efficacious than the 10 mg/day dose. Aripiprazole oral solution can be administered without regard to meals [se Clinical Studies (14.1)]. Patients should be periodically reassessed to Switching from Other Antipsychotics 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, more gradual discontinuation may be most appropriate for others. In all cases, the period of acceptance authorsychotic administration schould be miginized. overlapping antipsychotic administration should be minimized.

## 2.2 Bipolar I Disorder Acute Treatment of Manic and Mixed Episodes

Adults: The recommended starting dose in adults is 15 mg given once daily as monotherapy and 10 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 5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis mg/day, as monotherapy or as adjunctive therapy with lithium or valproate. The dose may be increased to 30 mg/day based on clinical response. The safety of doses above 30 mg/day has not been evaluated in clinical trials. Pediatrics: The recommended starting dose in pediatric patients (10 to 17 years) as monotherapy is 2 mg/day, with titration to 5 mg/day after 2 days, and a target dose of 10 mg/day after 2 additional days. Recommended dosing as adjunctive therapy to lithium or valproate is the same. Subsequent dose increases, if needed, should be administered in 5 mg/day increments. Aripiprazole oral Alzheimer's Disease solution can be given without regard to meals [see Clinical Studies (14.2)]. 2.3 Adjunctive Treatment of Major Depressive Disorder

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

reassessed to determine the continued need for maintenance treatment.

# Neuroleptic Malignant Syndrome: Manage with immediate discontinuation and close monitoring (5.4) Tardive Dyskinesia: Discontinue if clinically appropriate (5.5) 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 articipatestics (5.6)

- Weight Gain: Weight gain has been observed with atypical antipsychotic use. Monitor weight (5.6) weight carn. Weight gain tas been observed with adjusta altipsychoid case. Mortion weight (5.0) 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 creebrovascular disease, and risk of dehydration or syncope (5.8) Leukopenia, Neutropenia, and Agranulocytosis: have been reported with antipsychotics including aripiprazole. Patients with a history of a clinically significant low white blood cell count (WBC) or a drug-induced buttonesis by the control of the c
- leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of aripiprazole should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors (5.10) Seziumes/Convulsions: Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold (5.11)

  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 5.4 Neuroleptic Malignant Syndrome (NMS)
- -- ADVERSE REACTIONS ----Commonly observed adverse reactions (incidence  $\geq$ 5% and at least twice that for placebo) were (6.1):
- Adult patients with schizophrenia: akathisia Pediatric patients (13 to 17 years) with schizophrenia; extrapyramidal disorder, somnolence, and tremor Adult patients (monotherapy) with bipolar mania: akathisia, sedation, restlessness, tremor, and extrapyramidal disorder Adult patients (adjunctive therapy with lithium or valproate) with bipolar mania: akathisia, insomnia, and Pediatric patients (10 to 17 years) with bipolar mania: somnolence, extrapyramidal disorder, fatigue, nausea,
- Feduatic patients (10 to 17 years) with opical manua. Sommore, extrapyramidal disorder, radigue, nadsea, akathisia, blurred vision, salivary hypersecretion, and dizziness
   Adult patients with major depressive disorder (adjunctive treatment to antidepressant therapy): akathisia, restlessness, insommia, constipation, fatigue, and blurred vision
   Pediatric patients (6 to 17 years) with autistic disorder: sedation, fatigue, vomiting, somnolence, tremor, pyrexia, drooling, decreased appetite, salivary hypersecretion, extrapyramidal disorder, and lethargy
   Pediatric patients (6 to 18 years) with Tourette's disorder: sedation, somnolence, nausea, headache, association, processed appetite.

## To report SUSPECTED ADVERSE REACTIONS, contact Quagen Pharmaceuticals at 1-888-344-9603 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

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

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

# 8 USE IN SPECIFIC POPULATIONS

- 8.4 Pediatric Use 8.5 Geriatric Use 8.6 CYP2D6 Poor Metabolizers
- 8.7 Hepatic and Renal Impairm 8.8 Other Specific Populations 9 DRUG ARUSE AND DEPENDENCE

high-risk patients (5.14)

- 9.1 Controlled Substance 9.2 Abuse 9.3 Dependence
- 10 OVERDOSAGE 0.1 Human Experience
- 10.2 Management of Overdosage 11 DESCRIPTION 12 CLINICAL PHARMACOLOGY
- 12.1 Mechanism of Action 12.2 Pharmacodynamics 12.3 Pharmacokinetics
- 13 NONCLINICAL TOXICOLOGY
- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility 13.2 Animal Toxicology and/or Pharmacology 14 CLINICAL STUDIES
- 4.1 Schizophrenia 4.2 Bipolar Disorder 4.3 Adjunctive Treatment of Major Depressive Disorder 14.4 Irritability Associated with Autistic Disorder

#### 14.5 Tourette's Disorder 16 HOW SUPPLIED/STORAGE AND HANDLING

\*Sections or subsections omitted from the full prescribing information are not listed.

# 2.4 Irritability Associated with Autistic Disorder

Pediatric Patients (6 to 17 years) The recommended dosage range for the treatment of pediatric patients with irritability associated with autistic disorder is 5 to 15 mg/day. Dosing should be initiated at 2 mg/day. The dose should be increased to 5 mg/day, with subsequent increases to 10 or 15 mg/day if needed. Dose adjustments of up to 5 mg/day should occur gradually, at intervals of no less than 1 week [see Clinical Studies (14.4)]. Patients should be periodically eassessed to determine the continued need for maintenance treatment.

2.5 Tourette's Disorder Pediatric Patients (6 to 18 years) The recommended dosage range for Tourette's Disorder is 5 mg/day to 20 mg/day. For patients weighing less than 50 kg, dosing should be initiated at 2 mg/day with a target dose of 5 mg/day after 2 days. The dose can be increased to 10 mg/day in patients who do not achieve optimal control of tics. Dosage adjustments should occur gradually at intervals of no less than 1 week.

or patients weighing 50 kg or more, dosing should be initiated at 2 mg/day or 2 days, and then increased to 5 mg/day for 5 days, with a target dose of 0 mg/day on day 8. The dose can be increased up to 20 mg/day for patients who do not achieve optimal control of tics. Dosage adjustments should occur gradually in increments of 5 mg/day at intervals of no less than 1 week [see Patients should be periodically reassessed to determine the continued need

or maintenance treatment tive Treatment of Major Depressive Disorder [see Clinical Studies 2.7 Dosage Adjustments for Cytochrome P450 Considerations

Dosage adjustments are recommended in patients who are known CYP2D6 poor metabolizers and in patients taking concomitant CYP3A4 inhibitors or CYP2D6 inhibitors or strong CYP3A4 inducers (see Table 2). When the co-administered drug is withdrawn from the combination therapy, aripiprazole oral solution dosage should then be adjusted to its original level. When the co-administered 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 a favorable clinical response Table 2: Dose Adjustments for Aripiprazole Oral Solution in Patients who are known CYP2D6 Poor Metabolizers and Patients Taking Concomitant CYP2D6 Inhibitors, 3A4 Inhibitors, and/or CYP3A4 Inducers

inister half of usual dose inister a quarter of usual dose
inister a quarter of usual dose
ninister half of usual dose
inister a quarter of usual dose
ole usual dose over 2 weeks
ŀ

**2.8 Dosing of Oral Solution**The oral solution can be substituted for tablets on a mg-per-mg basis up to the 25 mg dose level. Patients receiving 30 mg tablets should receive 25 mg of drug effect on suicide. the solution [see Clinical Pharmacology (12.3)]. 3 DOSAGE FORMS AND STRENGTHS

Aripiprazole oral solution (1 mg/mL) is a clear, colorless to pale yellow solution, supplied in child - resistant bottles along with a calibrated oral dosing cup. 4 CONTRAINDICATIONS Anpiprazole oral solution is contraindicated in patients with a history of a hypersensitivity reaction to aripiprazole. Reactions have ranged from pruritus/urticaria to anaphylaxis [see Adverse Reactions (6.2)].

5 WARNINGS AND PRECAUTIONS Increased Mortality Elderly patients with dementia-related psychosis treated with sychotic drugs are at an increased risk of death. Aripiprazole is not oved for the treatment of patients with dementia-related psychosis

Safety Experience in Elderly Patients with Psychosis Associated with 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%], excessive salivation [placebo 0%, aripiprazole 4%], and interest contents of the property of the placebo 0%, aripiprazole 4%], and The safety and efficacy of aripiprazole in the treatment of patients with osychosis associated with dementia have not been established. If the rescriber elects to treat such patients with ariniprazole, assess for the

5.2 Cerebrovascular Adverse Events, Including Stroke In placebo-controlled clinical studies (two flexible dose and one fixed dose study) of dementia-related psychosis, there was an increased incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack), significant dose response relationship for cerebrovascular adverse events in patients treated with aripiprazole. Aripiprazole is not approved for the

treatment of patients with dementia-related psychosis [see Boxed 5.3 Suicidal Thoughts and Behaviors in Children, Adolescents, and 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. mg/dL (n=42) and +9.6 mg/dL (n=28), respectively with MDD, Obsessive Compulsive Disorder (OCD), or other psychiatric The mean change in fasting glucose in adjunctive aripigrazole-treated patients with

The pooled analyses of placebo-controlled trials in children and adolescents with MIDD, obsestive Commissive Distorted (VDD), 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 microbid trials in over 77,000 patients. There was considerable variation in risk of microbid the properties of the suicidality among drugs, but a tendency toward an increase in the younge patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1,000 Patients Treated
	Increases Compared to Placebo
<18	14 additional cases
18 to 24	5 additional cases
	Decreases Compared to Placebo
25 to 64	1 fewer case
≥65	6 fewer cases

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

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

he following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, veness, impulsivity, akathisia (psychomotor restle nia, and mania, have been reported in adult and pediatric patient hyporhalia, and maila, liave been reported in adult and pediation patients being treated with antidepressants for MDD as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the mergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depressi persistently worse, or who are experiencing emergent suicidality or symp that might be precursors to worsening depression or suicidality, especia

these symptoms are severe, abrupt in onset, or were not part of the patient's

presenting symptoms. Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the preparation of control to the control to the programs of control to the control

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

45 days, except for placebo-freated patients with baseline normal fasting LDL measurements, who had median treatment exposure of 24 days and HDL days, including aripiprazole. Rare cases of NMS occurred during aripiprazole. Table 9: Change in Blood Linid Parameters From Placebo-Controlled treatment in the worldwide clinical database. Clinical manifestations of NMS are uredurient in the workwise clinical adaptase; clinical tradities 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

potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported. 5.5 Tardive Dyskinesia A syndrome of potentially irreversible, involuntary, dyskinetic movements may

develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the Table 10 shows the proportion of patients with changes in total cholesterol respond to ambigorous a scaling that are the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

(fasting/nonfasting), fasting triglycerides, fasting LDL cholesterol, and HDL cause tardive dyskinesia is unknown. The risk of developing tardive dyskinesia and the likelihood that it will become major depressive disorder (median exposure 42 days). irreversible are believed to increase as the duration of treatment and the total

sumulative dose of antipsychotic drugs administered to the patient increas

Revised: 09/25 However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

Tardive dyskinesia may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and, thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown. Given these considerations, aripiprazole should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chroni antipsychotic treatment should generally be reserved for patients who suffe from a chronic illness that (1) is known to respond to antipsychotic drugs and (2) for whom alternative, equally effective, but potentially less harmful reatments 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. ff signs and symptoms of tardive dyskinesia appear in a patient on aripiprazole,

Table 11 shows the proportion of adolescents with schizophrenia (13 to 17) require treatment with aripiprazole despite the presence of the syndrome. 5.6 Metabolic Changes Atypical antipsychotic drugs have been associated with metabolic changes two placebo-controlled trials; median exposure 42 to 44 days).

Applical analysycholder drugs have been associated with inetabolic changes that include hyperglycemia/diabetes mellitius, 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. <u>Hyperglycemia/Diabetes Mellitus</u> Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical hyperosinolar control of death, has been reported in patients treated with anylocal 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

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 vs. 0/12 (0%); Fasting Triglycerides, 1/47 (2.1%) vs. 1/10 (10%), respectively. of diabetes) who are starting treatment with atypical antipsychotics should

Table 12 shows the proportion of patients with changes in total cholesterol undergo fasting blood glucose testing at the beginning of treatment and hyperglycemia during treatment with atypical antipsychotics should underg fasting blood glucose testing. In some cases, hyperglycemia has resolved whe the atvoical antinsychotic was discontinued; however some nationts requir continuation of anti-diabetic treatment despite discontinuation of the suspect dr

Adults
In an analysis of 13 placebo-controlled monotherapy trials in adults, primarily with schizophrenia or bipolar disorder, the mean change in fasting glucose in 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 ariniprazol rectain exposure 22 adys, in-1391, lable 3 shows the pulpor until a hiphracore - treated patients with normal and borderline fasting glucose at baseline (median exposure 25 days) that had treatment-emergent high fasting glucose measurements compared to placebo-treated patients (median exposure 22 days).

Table 6: Changes in Fasting Glucose From Placebo-Controlled Monotherapy Trials in Adult Patients				
	Category Change (at least once) from Baseline	Treatment Arm	n/N	%
Fasting Glucose	Normal to High (<100 mg/dL to	Aripiprazole	31/822	3.8
	≥126 mg/dL)	Placebo	22/605	3.6
	Borderline to High (≥100 mg/dL and	Aripiprazole	31/176	17.6
	<126 mg/dL to ≥126 mg/dL)	Placebo	13/142	9.2
	, the mean change in not significantly different			

Table 7: Changes in Fasting Glucose From Placebo-Controlled Adjunctive Trials in Adult Patients with Major Depressive Disorder				
	Category Change (at least once) from Baseline	Treatment Arm	n/N	%
	Fasting Glucose    Normal to High (<100 mg/dL to ≥ 126 mg/dL)   Borderline to High (≥100 mg/dL and <126 mg/dL to ≥ 126 mg/dL)	Aripiprazole	2/201	1
Eacting		Placebo	2/204	1
		Aripiprazole	4/34	11.8
		Placebo	3/37	8.1

Pediatric Patients and Adolescents In an analysis of two placebo-controlled trials in adolescents with schizophrenia (13 weight by indication. 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 with Weight Gain ≥ 7% of Body Weight

Tootmant

Tootmant

Tootmant 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 adolescen 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 natients with Tourette's disorder (6 to 19 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 of patients will changes in fashing 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 Adol Category Change Indication and Bipolar Disorder Irritability Associated with Autistic Disorder ≥126 mg/dL) Tourette's Disorder Fasting Glucos and Bipolar Disorder

with Autistic Disorder

Tourette's Disorder

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 my/dL (n=81) and +0.1 mg/dL (n=15), respectively]. Dvslipidemia Undesirable alterations in lipids have been observed in patients treated with

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 episode patients in the proportion with changes from normal to clinically significant levels for fasting/nonfasting total cholesterol, fasting triglycerides, fasting LDLs, and fasting/nonfasting HDLs. Analyses of patients with at least 12 or 24

history, including a family history of suicide, bipolar disorder, and depression. It should be noted that aripiprazole is not approved for use in treating depression in the pediatric population.

| Approved for use in treating depression in the pediatric population. | Approved for use in treating depression in the pediatric population. | Approved for use in treating depression in the pediatric population. | Approved for use in treating depression in the pediatric population. | Approved for use in treating depression in the pediatric population. | Approved for use in treating depression in the pediatric population. | Approved for use in treating depression in the pediatric population. | Approved for use in treating depression in the pediatric population. | Approved for use in treating depression in the pediatric population. | Approved for use in treating depression in the pediatric population. | Approved for use in treating depression in the pediatric population. | Approved for use in treating depression in the pediatric population. | Approved for use in treating depression in the pediatric population. | Approved for use in treating depression in the pediatric population. | Approved for use in treating depression in the pediatric population. | Approved for use in treating depression in the pediatric population | Approved for use in treating depression | days), fasting LDL cholesterol (pooled from eight trials; median exposure 39 to 45 days, except for placebo-treated patients with baseline normal fasting LDL Table 9: Changes in Blood Lipid Parameters From Placebo-Controlled

Monotherapy Trials in Adults Aripiprazole 34/1357 2.5 Aripiprazole 40/539 7.4 <150 mg/dL to ≥200 mg/dL) Placebo 30/431 7.0 2/332 0.6 Fasting LDL Cholesterol Aripiprazole <100 mg/dL to ≥160 mg/dL) Placebo 2/268 0.7

any concomitant serious medical problems for which specific treatments are any concommant senioris meucan protection of which specific pharmacological available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

In monotherapy trials in adults, the proportion of patients at 12 weeks and 24 weeks with changes from Normal to High in total cholesterol fra patient requires antipsychotic drug treatment after recovery from NMS, the (tasting/nonfasting), Tasting triglycendes, and fasting LDL cholesterol were similar between aripiprazole-and placebo-treated patients: at 12 weeks, Total Cholesterol (fasting/nonfasting), 1/71 (1.4%) vs. 3/74 (4.1%): Fasting result in harm to the patient and others if not recognized. Consider dose reduction or stopping the medication if a patient develops such urges. similar between ampiprazone-and placebor-tereated patients: at 12 weeks, lotal cholesterol (fasting/nontasting), 171 (1.4%) vs. 3/74 (4.1%); Fasting Triglycerides, 8/62 (12.9%) vs. 5/37 (13.5%); Fasting LDL Cholesterol, 0/34 (0%) vs. 1/25 (4%), respectively; and at 24 weeks, Total Cholesterol (rasting/nonfasting), 1042 (2.4%) vs. 3/37 (8.1%); Fasting Triglycerides, 5/34 aripirazole may cause orthostatic hypotension, perhaps due to its  $\alpha_1$ -dripirazole may cause orthostatic hypotension-associated events from short-term, placebo-controlled trials of adult patients on

Table 10: Changes in Blood Lipid Adjunctive Trials in Adult			
	Treatment Arm	n/N	%
Total Cholesterol Normal to High	Aripiprazole	3/139	2.2
(<200 mg/dL to ≥240 mg/dL)	Placebo	7/135	5.2
Fasting Triglycerides Normal to High	Aripiprazole	14/145	9.7
(<150 mg/dL to ≥200 mg/dL)	Placebo	6/147	4.1
Fasting LDL Cholesterol Normal to High	Aripiprazole	0/54	0
(<100 mg/dL to ≥160 mg/dL)	Placebo	0/73	0
HDL Cholesterol Normal to Low	Aripiprazole	17/318	5.3
Normal to Low (≥40 mg/dL to <40 mg/dL)	Placebo	10/286	3.5

tion should be considered. However, some patients may with aripiprazole despite the presence of the syndrome. With some proportion of adolescents with scinziplinia (1.5 or 1.5 o Table 11: Changes in Blood Lipid Parameters From Placebo-Controlled

Monotherapy Trials in Pediatric and Adolescent Patients in Schizophrenia and Bipolar Disorder Aripiprazole 3/220 <170 mg/dL to ≥200 mg/dL) Placebo 0/116 0 Aripiprazole 7/187 3.7 Fasting Triglycerides
Normal to High
(<150 mg/dL to ≥200 mg/dL)

Placebo HDL Cholesterol Aripiprazole 27/236 11.4 5.11 Seizures/Convulsions Normal to Low (≥40 mg/dL to <40 mg/dL) Placebo 22/109 20.2 In monotherapy trials of adolescents with schizophrenia and pediatric patient the atypical antipsychotics. Because aripiprazole was not marketed at the time with bipolar disorder the proportion of patients at 12 weeks with patients (6 to 18 years) 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.

a s a, of	(fasting/nonfasting) and fasting triglyce cholesterol (median exposure 55 to 56 pediatric patients (6 to 17 years) with	days) from two place	ebo-controllec	l trials
0 n	Table 12: Changes in Blood Lipid Trials in Pediatric Patien			ntroll
d		Treatment Arm	n/N	%
g.	Total Cholesterol Normal to High (<170 mg/dL to ≥200 mg/dL) Fasting Triglycerides Normal to High	Aripiprazole	1/95	1.1
h		Placebo	0/34	0
n		Aripiprazole	0/75	0
	(<150 mg/dL to ≥200 mg/dL)	Placebo	0/30	0
e	HDL Cholesterol Normal to Low (≥40 mg/dL to <40 mg/dL)	Aripiprazole	9/107	8.4
n		Placebo	5/49	10.

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

monitoring of weight is recommended.

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=1,673) compared to-0.1 kg (N=1,100) 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. In the trials adding aripiprazole to antidepressants, patients first received 8 weeks of antidepressant treatment followed by 6 weeks of adjunctive aripiprazole or placebo in addition to their ongoing antidepressant treatment.

The mean change in body weight in patients receiving adjunctive aripiprazole was +1.7 kg (N=347) compared to +0.4 kg (N=330) in patients receiving Table 14 shows the percentage of adult patients with weight gain  $\geq$  7% of body

eatment N Patients Weight gain ≥7% of body Bipolar Mania† Aripiprazole 719 16 (2 Major Depressive Disorder (Adjunctive Therapy) † Aripiprazole 347 | 18 (5.2)

\* 4 to 6 weeks duration. † 3 weeks duration. ‡ 6 weeks duration. Pediatric Patients and Adolescents In an analysis of two placebo-controlled trials in adolescents with schizophrenia (13 to 17 years) and pediatric patients with bipolar disorder (10 to 17 years) with median exposure of 42 to 43 days, the mean change in body weight in 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 aripiprazole had at least 1 year of exposure. In two short-term, placebo-controlled trials in patients (6 to 17 years) with

Tourette's Disorder with median exposure of 57 days, the mean change in body weight in aripiprazole-treated patients was  $+1.5~{\rm kg}~(n=105)$ compared to +0.4 kg (n=66) in placebo-treated patients.

Table 15 shows the percentage of pediatric and adolescent patients with 6.1 Clinical Trials Experience weight gain ≥7% of body weight by indication Table 15: Percentage of Patients From Placebo-Controlled Monotherapy Trials in Pediatric and Adolescent Patients with Weight Gain ≥

Indication Placebo | 187 | 3 (1.6) Weight gain ≥7% of body Irritability Associated Aripiprazole 209 55 (26.3) with Autistic Disordert Placebo 98 7 (7.1) Aripiprazole 105 21 (20) Tourette's Disorder‡

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 which normalize for the fractural growth of peculiar bardens 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

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 aripiprazole. 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 Ost-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 HDL Cholesterol
Normal to Low
(≥40 mg/dL to <40 mg/dL)

Aripiprazole

Aripiprazole

121/1066

11.4

Placebo

121/1066

11.4

Placebo

121/1066

12.5

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

> oral aripiprazole (n=2,467) included (aripiprazole incidence, placebo incidence) orthostatic hypotension (1%, 0.3%), postural dizziness (0.5%, 0.3%), and syncope (0.5%, 0.4%), of pediatric patients 6 to 18 years of age (n=732) on oral aripiprazole included orthostatic hypotension (0.5%, 0.0%), postural dizziness (0.4%, 0.%), and syncope (0.2%, 0.%) [see Adverse Reactions (6.11)]. The incidence of a significant orthostatic change in blood pressure (defined as a decrease in systolic blood pressure ≥20 mmHg accompanied by an increase in heart rate ≥25 bpm when comparing standing to supine values) for aripiprazole was not meaningfully different from placebo (aripiprazole incidence, placebo incidence): in adult oral aripiprazole-treated patients (4%, 2%), or 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

5.9 Falls Antipsychotics, including aribiprazole may cause somnolence, nostural 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.

treatment with antihypertensive medications) [see Drug Interactions (7.1)].

5.10 Leukopenia, Neutropenia, and Agranulocytosis o. to Ecuatylerian, reductive and Agranutorytosis

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 thorapy. 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 symptom or signs of infection and treat promptly if such symptoms or signs of infection and treat promptly if such symptoms or signs occur. Discontinue anjpiprazole in patients with severe neutropenia (absolute neutrophil count <1,000/mm³) and follow their WBC counts until recovery.

neutrophil count <1,000/mm³) and follow their WBC counts until recovery.

5.11 Seizures/Convulsions
In short-term, placebo-controlled trials, patients with a history of seizures excluded seizures/convulsions occurred in 0.1% (3/2,467) of undiagnosed adult patients treated with oral aripiprazole, and in 0.1% (1/732) of pediatric patients (6 to 18 years).

patients with a history of seizures or with conditions that lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older. 5.12 Potential for Cognitive and Motor Impairment

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 seadation) was reported as follows (aripiprazole incidence, placebo incidence): in adult patients (n=2,467) treated ith oral aripiprazole (11%, 6%), and in pediatric patients ages 6 to 17 =611) (24%, 6%). Somnolence (including sedation) led to discontinuation in 0.3% (8/2,467) of adult patients and 3% (20/732) of pediatric patients (6 to 18 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

5.13 Body Temperature Regulation Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing autilities a disposition agents. Appropriate care is advised when prescribed arrippracel for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, (e.g., exercising strenuously exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration) [see Adverse Reactions (6.2)]. 5.14 Suicide

aripiprazole does not affect them adversely.

The possibility of a suicide attempt is inherent in psychotic illnesses, bipolar disorder, and major depressive disorder, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for aripiprazole should be written for the smallest quantity consistent with good patient management in order to reduce the risk of overdose [see Adverse Reactions (6.1, 6.2)]. 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 p [see Warnings and Precautions (5.1) and Adverse Reactions (6.2)]. 6 ADVERSE REACTIONS cause clinical trials are conducted under widely varying conditi adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The following adverse reactions are discussed in more detail in other Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Cerebrovascular Adverse Events, Including Stroke [see Warnings and Precautions (5.2)] uicidal Thoughts and Behaviors in Children, Adolescents, and Young Adults [see Boxed Warning and Warnings and Precautions (5.3)] Neuroleptic Malignant Syndrome (NMS) [see Warnings and Precautions (5.4)] Metabolic Changes [see Warnings and Precautions (5.6)] Pathological Gambling and Other Compulsive Behaviors [see Warnings

[see Boxed Warning and Warnings and Precautions (5.1)]

and Precautions (5.7)]
Orthostatic Hypotension [see Warnings and Precautions (5.8)] Falls [see Warnings and Precautions (5.9)] izures/Convulsions [see Warnings and Precautions (5.11)] otential for Cognitive and Motor Impairment [see Warnings and Precautions (5.12)]
Body Temperature Regulation [see Warnings and Precautions (5.13)]

Dysphagia [see Warnings and Precautions (5.15)] The most common adverse reactions in adult patients in clinical trials ( $\geq$ 10%) were nausea, vomiting, constipation, headache, dizziness, akathisia, anxiety, insomnia, and restlessness. The most common adverse reactions in the pediatric clinical trials (≥10%) were somnolence, headache, vomiting, extrapyramidal disorder, fatigue increased appetite, insomnia, nausea, nasopharyngitis, and weight increased Aripiprazole has been evaluated for safety in 13,543 adult patients who participated in multiple-dose, clinical trials in schizophrenia, bipolar disorder, major depressive disorder, Dementia of the Alzheimer's type, Parkitson's disease, and alcoholism, and who had approximately 7619 patient-years of exposure to oral aripiprazole. A total of 3,390 patients were treated with oral aripiprazole for at least 180 days and 1933 patients treated with oral aripiprazole for at least 1 year of exposure.

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.

Suicide [see Warnings and Precautions (5.14)]

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 was patients. We consider the patients was patients were treated with oral aripiprazole at least 180 days and 556 patients. The conditions and duration of treatment with aripiprazole (monotherapy and adjunctive therapy with antidepressants or mood stabilizers) included (i overlapping categories) double-blind, comparative and noncomparative open-label studies, inpatient and outpatient studies, fixed- and flexible-dose studies, and short-and longer-term exposure.

The following 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 mg/day to 30 mg/day.

Commonly Observed Adverse Reactions The only commonly observed adverse reaction associated with the use of aripiprazole incidence at least twice that for placebo) was akathisia (aripiprazole 8%: placebo 4%). Adult Patients with Bipolar Mania Monotherapy

The following findings are based on a pool of 3-week, placebo-controlled. bipolar mania trials in which oral aripiprazole was administered at doses of 15 4 to 6 weeks duration. † 8 weeks duration. ‡ 8 to 10 weeks duration. Commonly Observed Adverse Reactions

oonminoning oboon rou navoi	00 1104040110	
	ania (incidence of 5%	ed with the use of aripiprazolo 6 or greater and aripiprazolo wn in Table 16.
Controlled Trial		ons in Short-Term, Placebo with Bipolar Mania Treated
	Percentage of Pa	tients Reporting Reaction
	Aripiprazole	Placebo
Preferred Term	(n=917)	(n=753)
Akathisia	13	4
Sedation	8	3
Restlessness	6	3
Tremor	6	3
Extransmidal Disorder	5	2

Less Common Adverse Reactions in Adults Table 17 enumerates the pooled incidence, rounded to the nearest percent, of adverse reactions that occurred during acute therapy (up to 6 weeks in schizophrenia and up to 3 weeks in bipolar mania), including only those reactions that occurred in 2% or more of patients treated with 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

or conduction abnormalities), cerebrovascular disease, or conditions which would predispose patients to hypotension (dehydration, hypovolemia, and

Respiratory, Thoracic, and N Pharyngolaryngeal Pain 3 Cough 3 An examination of population subgroups did not reveal any clear evidence of

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 aripiprazole-treated compared o placebo-treated patients were akathisia (5% and 1%, respectively) and

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, and extrapyramidal disorder. Less Common Adverse Reactions in Adult Patients with Adjunctive Therapy in

Table 18 enumerates the incidence, rounded to the nearest percent, of advers radie to enumerates the inicialitie, fourhead to the fleasts percent, or 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 mg/day or 30 mg/day) and lithium or valproate and or which the incidence in patients treated with this combination was greate than the incidence in patients treated with placebo plus lithium or valproate Table 18: Adverse Reactions in a Short-Term, Placebo-Controlled Trial of

Dry Mouth Infections and Infestal

† Lithium or Valproate

Pediatric Patients (13 to 17 years) with Schizophrenia The following findings are based on one 6-week, placebo-controlled trial in which oral aripiprazole was administered in doses ranging from 2 mg/day to 30 Adverse Reactions Associated with Discontinuation of Treatmen eukopenia, Neutropenia, and Agranulocytosis [see Warnings and The incidence of discontinuation due to adverse reactions between 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

Aripiprazole has been evaluated for safety in 1,686 patients (6 to 18 years) who participated in multiple-dose, clinical trials in schizophrenia, bipolar

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

	i ciccinage of i attent	s ricporting ricacti
Preferred Term	Aripiprazole (n=197)	Placebo (n=97)
Somnolence	23	3
Extrapyramidal Disorder	20	3
Fatigue	11	4
Nausea	11	4
Akathisia	10	2
Blurred Vision	8	0
Salivary Hypersecretion	6	0
Dizziness	5	1

Pediatric Patients (6 to 17 years) with Autistic Disorder

The following findings are based on two 8-week, placebo-controlled trials in aripiprazole in patients with schizophrenia (incidence of 5% or greater and which oral aripiprazole was administered in doses of 2 mg/day 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

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

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

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. Commonly Observed Adverse Reactions

Commonly observed adverse reactions associated with the use of aripiprazole in pediatric patients with Tourette's disorder (incidence of 5% or greater and ripiprazole incidence at least twice that for placebo) are shown in Table 21. Table 21: Commonly Observed Adverse Reactions in Short-Term,
Placebo-Controlled Trials of Pediatric Patients (6 to 18 years)
with Tourette's Disorder Treated with Oral Aripiprazole

Percentage of Patients Reporting Reaction Headache Fatique Less Common Adverse Reactions in Pediatric Patients (6 to 18 years) with Table 22 enumerates the pooled incidence, rounded to the nearest percent, of adverse reactions that occurred during acute therapy (up to 6 weeks in schizophrenia, up to 4 weeks in bipolar mania, up to 8 weeks in autistic disorder, and up to 10 weeks in Tourette's disorder), including only those

reactions that occurred in 2% or more of pediatric patients treated with

aripiprazole (doses ≥2 mg/day) and for which the incidence in patients treated

with aripiprazole was greater than the incidence in patients treated with Table 22: Adverse Reactions in Short-Term, Placebo-Controlled Trials of Pediatric Patients (6 to 18 years) Treated with Oral Aripiprazole Percentage of Patients Reporting Reaction\* Eve Disorders Abdominal Pain Upper Metabolism and Nutrition Disord Decreased Annetite Musculoskeletal Stiffness

\*Adverse reactions reported by at least 2% of nediatric nations treated with cole, except adverse reactions which had an incidence equal to Adult Patients Receiving Aripiprazole as Adjunctive Treatment of Major Depressive Disorder The following findings are based on a pool of two placebo-controlled trials of patients with major depressive disorder in which aripiprazole was administered at doses of 2 mg to 20 mg as adjunctive treatment to continued antidepressant Adverse Reactions Associated with Discontinuation of Treatment

The commonly observed adverse reactions associated with the use of adjunctive aripiprazole in patients with major depressive disorder (incidence of 5% or greater and aripiprazole incidence at least twice that for placebo) were: akathisia, restlessness, insomnia, constipation, fatigue, and blurred vision. Less Common Adverse Reactions in Adult Patients with Major Depressive adverse reactions that occurred during acute therapy (up to 6 weeks), including only those adverse reactions that occurred in 2% or more of patients treated with adjunctive aripiprazole (doses ≥2 mg/day) and for which the

The incidence of discontinuation due to adverse reactions was 6% for

incidence in patients treated with adjunctive aripiprazole was greater than the incidence in patients treated with adjunctive placebo in the combined dataset Table 23: Adverse Reactions in Short-Term, Placebo-Controlled Adjunctive Trials in Patients with Major Depressive Disorder Eve Disorders Gastrointestinal Disorder General Disorders and Adı Metabolism and Nutrition Disorde

26 mg/dL)

had you talk

or less than placeb

52032 ARIPIPRAZOLE Oral Solution (Quagen)\_01

NOV 19, 2025 01:00 PM

### Dose-Related Adverse Reactions

**Schizophrenia** Dose response relationships for the incidence of treatment-emergent adverse Musculoskeletal and Connective Tissue Disorders: events were evaluated from four trials in adult patients with schizophrenia infrequent - muscular weakness, muscle tightness; rare - rhabdomyolysis, comparing various fixed doses (2 mg/day, 5 mg/day, 10 mg/day, 15 mg/day, 20 mobility decreased mg/day, 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 infrequent – aggression, loss of libido, delirium; rare – libido increased, relationship: extrapyramidal disorder (incidences were placebo, 5%; 10 mg, 13%; 30 mg, 21.6%); somnolence (incidences were placebo, 6%; 10 mg, 11%; 30 mg, 8 mg, 21.6%); somnolence (incidences were placebo, 6%; 10 mg, 11%; 30 mg, 11%; 30 mg, 21.6%); somnolence (incidences were placebo, 6%; 10 mg, 11%; 30 mg, 21.6%); somnolence (incidences were placebo, 6%; 10 mg, 11%; 30 mg, 21.6%); somnolence (incidences were placebo, 6%; 10 mg, 11%; 30 mg, 21.6%); somnolence (incidences were placebo, 6%; 10 mg, 11%; 30 mg, 21.6%); somnolence (incidences were placebo, 6%; 10 mg, 11%; 30 mg, 21.6%); somnolence (incidences were placebo, 6%; 10 mg, 11%; 30 mg, 21.6%); somnolence (incidences were placebo, 6%; 10 mg, 11%; 30 mg, 21.6%); somnolence (incidences were placebo, 6%; 10 mg, 11%; 30 mg, 21.6%); somnolence (incidences were placebo, 6%; 10 mg, 11%; 30 mg, 21.6%); somnolence (incidences were placebo, 6%; 10 mg, 11%; 30 mg, 21.6%); somnolence (incidences were placebo, 6%; 10 mg, 11%; 30 mg, 21.6%); somnolence (incidences were placebo, 6%; 10 mg, 11%; 30 mg, 21.6%); somnolence (incidences were placebo, 6%; 10 mg, 11%; 30 mg, 21.6%); somnolence (incidences were placebo, 6%; 10 mg, 11%; 30 mg, 21.6%); somnolence (incidences were placebo, 6%; 10 mg, 11%; 30 mg, 21.6%); somnolence (incidences were placebo, 6%; 10 mg, 11%; 30 mg, 21.6%); somnolence (incidences were placebo, 6%; 10 mg, 11%; 30 mg, 21.6%); somnolence (incidences were placebo, 6%; 10 mg, 11%; 30 mg, 21.6%); somnolence (incidences were placebo, 6%; 10 mg, 11%; 30 mg, 21.6%); somnolence (incidences were placebo, 6%; 10 mg, 11%; 30 mg, 21.6%); somnolence (incidences were placebo, 6%; 10 mg, 11%; 30 mg, 21.6%); somnolence (incidences were placebo, 6%; 10 mg, 21.6%); so 21.6%); and tremor (incidences were placebo, 2%; 10 mg, 2%; 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. 2.2%; 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 ma. 3.1%: 30 ma. 8.1%).

Autistic Disorder In a study of pediatric patients (6 to 17 years of age) with autistic disorder, one Vascular Disorders: common adverse reaction had a possible dose response relationship: fatigue infrequent – hypotension, hypertension (incidences were placebo, 0%; 5 mg, 3.8%; 10 mg, 22%; 15 mg, 18.5%).

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

Extrapyramidal Symptoms Schizophrenia In short-term, placebo-controlled trials in schizophrenia in adults, the incidence Gastrointestinal Disorders: of reported EPS-related events, excluding events related to akathisia, for infrequent - tongue dry, tongue spasm

aripiprazole-treated patients was 13% vs. 12% for placebo; and the incidence of Investigations: akathisia-related 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% Renal and Urinary Disorders: frequent – enuresis vs. 7% for placebo; and the incidence of akathisia-related events for aripiprazole Skin and Subcutaneous Tissue Disorders: infrequent - hirsutism Objectively collected data from those trials was collected on the Simpson Angus

Objectively collected data from those traits was ouriced on the simpost range.

Rating Scale (for EPS), the Barnes Akathisia Scale (for akathisia), and the Assessments of Involuntary Movement Scales (for dyskinesias). In the adult assessments of Involuntary Movement Scales (for dyskinesias). In the adult assessments of Involuntary Movement Scales (for dyskinesias). In the adult assessments of Involuntary Movement Scales (for dyskinesias). In the adult assessment of Involuntary Movement Scales (for dyskinesias). In the adult assessment of Involuntary Movement Scales (for dyskinesias). In the adult assessment of Involuntary Movement Scales (for dyskinesias) and the scale (for EPS) and the scale between aripiprazole 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 and placebo, with the exception of the Simpson Angus Rating Scale (aripiprazole, 0.24; placebo, –0.29).

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 betwee aripiprazole and placebo. Bipolar Mania

In the short-term, placebo-controlled trials in bipolar mania in adults, the incidence of reported EPS- related events, excluding events related to akathisia for monotherapy 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 reportec 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 Simpso Angus Rating Scale and the Barnes Akathisia Scale showed a significan

difference between aripiprazole and placebo (aripiprazole, 0.5; placebo, -0.01 and aripiprazole, 0.21; placebo, -0.05). Changes in the Assessments o 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, 0.3; 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 Based on pharmacokinetic studies, no dosage adjustment of aripiprazole is Scale showed a significant difference between arioiprazole and placebo required when administered concomitantly with famotidine, valproate, lithium, (aripiprazole, 0.9; placebo, -0.05). Changes in the Barnes Akathisia Scale and Iorazepam. sessments of Involuntary Movement Scales were similar for the In addition r

aripiprazole and placebo groups.

Major Depressive Disorder In the short-term, placebo-controlled trials in major depressive disorder, the incidence of reported EPS-related events, excluding events related to akathisia, for Additionally, no dosage adjustment is necessary for valproat adjunctive aripiprazole-treated patients was 8% vs. 5% for adjunctive lamotrigine, lorazepam, or sertraline when coadministered with aripiprazole placebo-treated patients; and the incidence of akathisia-related events for adjunctive

| See Clinical Pharmacology (12.3)|...
| See Cl In the maior depressive disorder trials, the Simpson Angus Rating Scale and the

8.1 Pregnancy Barnes Akathisia Scale showed a significant difference between adjunctive aripiprazole and adjunctive placebo (aripiprazole, 0.31; placebo, 0.03 and ariningazole 0.22 placeho 0.02) Changes in the Assessments of Involuntary ement Scales were similar for the adjunctive aripiprazole and adjunctive

placebo groups. Autistic Disorder In the short-term, placeho-controlled trials in autistic disorder in pediatric programs/pregne patients (b) of 17 years), the incidence of reported EPS-related events, excluding events related to akathisia, for aripiprazole-treated patients was 18% vs. 2% for Neported EPS-related events. 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.

Tourette's Disorder In the short-term, placebo-controlled trials in Tourette's disorder in pediatric patients (6 to 18 years), the incidence of reported EPS-related events, excluding events related to akathisia, for aripiprazole-treated patients was 7% vs. 6% for placebo and the incidence of akathisia-related events for aripiprazole-treated direction studies, oral and intravenous aripiprazole administration during organogenesis in rats and/or rabbits at doses 10 and 19 times, patients was 4% vs. 6% for placebo.

aripiprazole and placebo.

Dvstonia Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more

frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups. Additional Findings Observed in Clinical Trials Adverse Reactions in Long-Term, Double-Blind, Placebo-Controlled Trials The adverse reactions reported in a 26-week, double-blind trial comparing oral 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 placebol. 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 monotherapy study and a long-term adjunctive study with lithium and valproate in bipolar disorder. Other Adverse Reactions Observed During the Premarketing Evaluation of <u>Aripiprazole</u>

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

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 Data 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 Eve Disorders: infrequent - photophobia; rare - diplopia

Gastrointestinal Disorders: infrequent - gastroesophageal reflux disease General Disorders and Administration Site Conditions: frequent - asthenia: infrequent - peripheral edema, chest pain: rare - face edema Hepatobiliary Disorders: rare - hepatitis, jaundice

Immune System Disorders: rare - hypersensitivity Injury, Poisoning, and Procedural Complications: infrequent - fall: rare - heat stroke Investigations:

blood glucose increased, blood lactate dehydrogenase increased, gamma glutamyl transferase increased; rare - blood prolactin increased, blood urea

Metabolism and Nutrition Disorders: frequent - anorexia; rare - hypokalemia, hyponatremia, hypoglycemi

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

rare - urinary retention, nocturia

Reproductive System and Breast Disorders. infrequent - erectile dysfunction; rare - gynaecomastia, menstruation irregular, amenorrhea, breast pain, priapism Respiratory, Thoracic, and Mediastinal Disorders; infrequent - nasal congestion.

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

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 adult population.

infrequent - oculoavric crisis

frequent - blood insulin increased

Nervous System Disorders: infrequent - sleep talking

6.2 Postmarketing Experience The following adverse reactions have been identified during nost-approval use 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, and drug reaction with eosinophilia and systemic symptoms (DRESS) and fecal incontinence. 7 DRUG INTERACTIONS Similarly, in a long-term (26-week), placebo-controlled trial of schizophrenia in Similarly, in a long-term (26-week), placebo-controlled trial of schizophrenia in Schizophreni

Concomitant Drug Name or Drug Class	Clinical Rationale	Clinical Recommendation With concomitant use of aripiprazole with a strong CYP3A4 inhibitor or CYP2D6 inhibitor, reduce the aripiprazole dosage [see Dosage and Administration (2.7)].	
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)].		
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 aripiprazole with a strong CYP3A4 inducer, consider increasing the aripiprazole dosage [see 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 & 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	Monitor sedation and blood pressure. Adjust dose accordingly.	

7.2 Drugs Having No Clinically Important Interactions with Aripiprazole

(e.g., dextromethorphan, fluoxetine, paroxetine, or venlafaxine), CYP2C9 (e.g., warfarin), CYP2C19 (e.g., omeprazole, warfarin, escitalopram), or CYP3A4 Additionally, no dosage adjustment is necessary for valproate, lithium,

Pregnancy Exposure Registry 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-research-

Neonates 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 atta from published epidemiologic studies of pregnant women exposed to aripiprazole have not established a drug-associated risk of major birth defects, and most of the drug effects in juvenile rats were also 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 Iniscarriage, or adverse material or lead outcomes (see Data). There are its so to the mother associated with untreated schizophrenia, bipolar I disorder, or major depressive disorder, and with exposure to antipsychotics, including aripiprazole, during pregnancy (see Clinical Considerations). Aripiprazole administered orally for 6 months at 3, 10, 30 mg/kg/day. Mean body weight and exposure during pregnancy can have variable effects on milk supply in the post-partum period [see Use in Specific Populations (8.2)].

in alimia reproduction studies, that and intravenous aripphazone 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 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 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.

Clinical Considerations Disease-associated maternal and/or embryo/fetal risk There is a risk to the mother from untreated schizophrenia or bipolar I disorder. including increased risk of relapse, hospitalization, and suicide. Schizophrenia and bipolar I disorder are associated with increased adverse perinatal outcomes, including preterm birth. It is not known if this is a direct result of

the illness or other comorbid factors.

A prospective, longitudinal study followed 201 pregnant women with a history of major depressive disorder who were euthymic and taking antidepressants at the beginning of pregnancy. The women who discontinued antidepressants during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressants. Consider the risk of untreated depression when discontinuing or changing treatment with antidepressant medication during pregnancy and postpartum.

Fetal/Neonatal Adverse Reactions Extrapyramidal and/or withdrawal symptoms, including agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder have been reported in neonates who were exposed to antipsychotic drugs (including 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 treatment; others required prolonged hospitalization.

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 9,258 women exposed to antipsychotics during 10 OVERDOSAGE pregnancy did not indicate an overall increased risk for major birth defects. 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. Delivered offspring had ncreased incidences of hepatodiaphragmatic nodules and diaphragmatic herni increased incuences of reparadiagnization footing and dispinagnization may were observed at 10 times the MRHD (the other dose groups were not examined for these findings). Postnatally, delayed vaginal opening was seen at 3 and 10 times the MRHD. Impaired reproductive performance (decreased fertility rate, corpora lutea, implants, live fetuses, and increased post-implantation loss, likely 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. lethargy, loss of consciousness, QRS complex prolonged, QT prolonged,

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 pneumonia aspiration, respiratory arrest, status epilepticus, and tachycardia ng/day based on mg/m² body surface area, decreased fetal weight and

elayed skeletal ossification were observed at 9 times the MRHD; this dose 10.2 Management of Overdosage 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, and if CT interval prolongation is present, cardiac monitoring should be decreased maternal food consumption, and increased abortions as well as 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 noreased fetal mortality were observed at 65 times the MRHD. Decreased fetal mortality were observed at 65 times the MRHD. Decreased fetal mortality were observed at 65 times the MRHD. Decreased fetal mortality were observed at 65 times the MRHD. weight and increased incidence of fused sternebrae were observed at 19 and

in pregnant rabust injected intervenously with application during trigingleness 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 naternal toxicity. The fetal no-effect dose was 10 mg/kg/day, which is 6 times In rats treated orally with aripiprazole peri-and post-natally from destation day

7 through postpartum day 21 at doses of 3 10 and 30 mg/kg/day which are 17 intough buspan that yet a way to use so is 7, in an ost migray 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 MRHD. An increase in stillbirths and, decreases in pup weight (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 loses also caused some maternal toxicity. There were no effects on postnatal vioral and reproductive development 8.2 Lactation

Aripiprazole is present in human breast milk. Based on published case reports and pharmacovigilance reports, aripiprazole exposure during pregnancy and/or the nostnartum period can lead to variable effects on milk supply in the post-partum 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 prolation 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 Clinical Considerations

fonitor infants exposed to aripiprazole through breastmilk for dehydration and ack of appropriate weight gain. 8.4 Pediatric Use Safety and effectiveness in pediatric patients with major depressive disorder or agitation associated with schizophrenia or bipolar mania have not been

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 Peactions (6.1), and Clinical Studies (14.1). Although maintenance efficacy in pediatric patients has not been systematically evaluated, maintenance efficacy can be extrapolated from adult data along with comparisons of aripiprazole pharmocolistic appropriate in adult data along with comparisons of aripiprazole pharmocolistic appropriate. pharmacokinetic parameters in adult and pediatric patients.

Bipolar I Disorder

Safety and effectiveness in pediatric patients with bipolar mania were ORAL ADMINISTRATION 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 physical properties of the harmacokinetic parameters in adult and pediatric patients. he efficacy of adjunctive aripiprazole with concomitant lithium or valproate in nteraction between aripiprazole and lithium or valproate can be extrapolated

from adult data, along with comparisons of aripiprazole pharmacokinetic ritability Associated with Autistic Disorder Safety and effectiveness in pediatric patients demonstrating irritability associated with autistic disorder were established in two 8-week inlaceho-controlled clinical (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 vas an open-label, flexibly dosed (aripiprazole 2 mg/day to 15 mg/day) phase in which patients were stabilized (defined as > 2% improvement on the ABC-I subscale, and a GGI-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

Safety and entertureless or appliazone in pediatric patients with floating 25% and 55 bisorder 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 the frees. pediatric patients has not been systematically evaluated.

Juvenile Animal Studies Aripiprazole in juvenile rats caused mortality, CNS clinical signs, impaired memory and learning, and delayed sexual maturation when admin stered at oral loses of 10, 20, 40 mg/kg/day from weaning (21 days old) through maturity (80 days old). At 40 mg/kg/day, mortality, decreased activity, splayed hind limbs, hunched posture, ataxia, tremors and other CNS signs were observed in both genders. In addition, delayed sexual maturation was observed in males. At all doses and in a dose-dependent manner, impaired memory and learning, ncreased motor activity, and histonathology changes in the nituitary (atrophy) adrenals (adrenocortical hypertrophy), mammary glands (hyperplasia and increased secretion), and female reproductive organs (vaginal mucification, endometrial atrophy, decrease in ovarian corpora lutea) were observed. The changes in female reproductive organs were considered secondary to the ncrease in prolactin serum levels. A No Observed Adverse Effect Level (NOAEL) could not be determined and, at the lowest tested dose of 10 mg/kg/day, there observed in adult rats from previously conducted studies. ontrol values. A NOAEL could not be determined and, at the lowest tested dose

weight gain were decreased up to 18% in females in all drug groups relative to of 3 mg/kg/day, there is no safety margin relative to the systemic exposures  $(AUC_{p,3b})$  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 No 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, 1,073 (8%) were ≥65 years old and 799 (6%) were ≥75 years old. Placebo-controlled

studies of oral aripiprazole in schizophrenia, bipolar mania, or major depressive disorder did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from vounger subjects. Aripiprazole is not approved for the treatment of patients with psychosis associated with Alzheimer's disease [see Boxed Warning and Warnings and 8.6 CYP2D6 Poor Metabolizers

Dosage adjustment is recommended in known CYP2D6 poor metabolizers due to high aripiprazole concentrations. Approximately 8% of Caucasians and 3% 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)]. 8.7 Hepatic and Renal Impairment

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)].

8.8 Other Specific Populations No dosage adjustment for aripiprazole is required on the basis of a patient's sex, race, or smoking status [see Clinical Pharmacology (12.3)]. 9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance Aripiprazole is not a controlled substance.

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).

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

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 1,260 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

instituted. Otherwise, management of overdose should concentrate on Gender female vs. male supportive therapy, maintaining an adequate airway, oxygenation and ventilation, and management of symptoms. Close medical supervision and Age 18-64 vs. >65 years old nonitoring should continue until the patient recovers. Charcoal: In the event of an overdose of aripiprazole, an early charcoal Hepatic Impairment: mild vs. normal mild vs. normal administration may be useful in partially preventing the absorption of aripiprazole. Administration of 50 g of activated charcoal, one hour after single 15 mg oral dose of aripiprazole, decreased the mean AUC and C<sub>max</sub> of

aripiprazole by 50%. Hemodialysis: Although there is no information on the effect of hemodialysis in treating an overdose with ariniprazole, hemodialysis is unlikely to be useful in overdose management since aripiprazole is highly bound to plasma proteir 11 DESCRIPTION Aripiprazole, USP is an atypical antipsychotic drug that is available as an

N-CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>O Aripiprazole Oral Solution is a clear, colorless to pale yellow solution available

in a concentration of 1 mg/mL. The inactive ingredients for this solution include edetate disodium dihydrate, fructose, glycerin, malic acid, methylparaben, propylene glycot, propylparaben, purified water, sodium hydroxide and sucrose. The Oral Solution is flavored with natural and artificial orange flavor. 12 CLINICAL PHARMACOLOGY

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 5-HT $_{1A}$  receptors and antagonist activity at 5-HT $_{2A}$  receptors. 12.2 Pharmacodynamics

the serotonin reuptake site ( $K_1$ =98 nM). Aripiprazole has no appreciable affinity for cholinergic muscarinic receptors ( $IC_{sn}$ >1,000 nM). for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unclear.

12.3 Pharmacokinetics 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)].

The mutagenic potential of aripiprazole was tested in the *in vitro* bacterial DNA repair assay, the *in vitro* for the differences in body weight [see Clinical Pharmacology (12.3)].

The mutagenic potential of aripiprazole was tested in the *in vitro* bacterial DNA repair assay, the *in vitro* bacterial DNA repair assay, the *in vitro* sarpiprazole, and to a lesser extent, to its major metabolite, dehydro-aripiprazole was tested in the *in vitro* bacterial DNA repair assay, the 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

Elimination of aripiprazole is mainly through hepatic metabolism involving two P450 isozymes, CYP2D6 and CYP3A4. For CYP2D6 poor metabolizers, assay in mice; however, the response was due to a mechanism not considered the mean elimination half-life for aripiprazole is about 146 hours

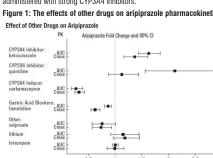
Absorption
Oral Solution: Aripiprazole is well absorbed when administered orally as the solution. At equivalent doses, the plasma concentrations of aripiprazole from the solution were higher than that from the tablet formulation. In a surface area. Estrus cycle irregularities and increased corpora lutea were 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<sub>max</sub> and AUC values were 122% and 114%, respectively *[see Dosage and Administration]*Male rats were treated orally with aripiprazole from 9 weeks prior to mating (2.6)]. The single-dose pharmacokinetics of aripiprazole were linear and dose-proportional between the doses of 5 mg to 30 mg. Distribution

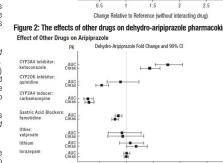
The steady-state volume of distribution of aripiprazole following intravenous The steady-state volume of distribution of an pipirazole following intraversious administration is high (404 Lor 4.9 L/Kg), indicating extensive extravascular distribution. At therapeutic concentrations, aripiprazole and its major metabolite are greater than 99% bound to serum proteins, primarily to albumin. In healthy human volunteers administered 0.5 mg/day to 30 mg/day and aripiprazole for 14 days, there was dose-dependent D<sub>2</sub> receptor occupancy indicating study at doses of 40 mg/kg and 60 mg/kg. The 40 brain penetration of aripiprazole in humans. Metabolism and Elimination Aripiprazole is metabolized primarily by three biotransformation pathways:

efficacy of aripiprazole for the maintenance treatment of irritability associated and feces, respectively. Less than 1% of unchanged aripiprazole was excreted in the urine and approximately 18% of the oral dose was recovered unchanged

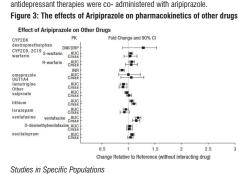
> Drug Interaction Studies Effects of other drugs on the exposures of aripiprazole and dehydro-aripiprazole are summarized in Figure 1 and Figure 2, respectively. Based on simulation, a 4.5-fold increase in mean  $C_{\mbox{\scriptsize max}}$  and AUC values at steady-state is expected when extensive metabolizers of CYP2D6 are administered with ooth strong CYP2D6 and CYP3A4 inhibitors. A 3-fold increase in mean C and AUC values at steady-state is expected in poor metabolizers of CYP2D6 administered with strong CYP3A4 inhibitors.

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





Change Relative to Reference (without interacting drug) The effects of aripiprazole on the exposures of other drugs are summarized in Figure 3. A population PK analysis in patients with major depressive disorder showed no substantial change in plasma concentrations of fluoxetine (20 or 40 mg/day), paroxetine CR (37.5 or 50 mg/day), or sertraline (100 or 150 mg/day) dosed to steady-state. The steady-state plasma concentrations of fluoxetine and norfluoxetine increased by about 18% and 36%, respectively, and concentrations of paroxetine decreased by about 27%. The steady-state plasma concentrations of sertraline and desmethylsertraline were not substantially changed when these antidepressant therapies were co- administered with aripiprazole.



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 Pediatric Patients mg), the body weight corrected aripiprazole clearance was similar to the adults. Figure 4: Effects of intrinsic factors on Aripiprazole pharmacokinetics

-\_\_\_\_ moderate vs. normal - Figure 5: Effects of intrinsic factors on dehydro-aripiprazole pharmacokinetics: Table 26: Schizophrenia Studies ---CMAY - -\_\_\_

13 NONCLINICAL TOXICOLOGY Aripiprazole Oral Solution, Aripiprazole, USP is7-[4-[4-(2,3-dichlorophenyl)]

-1-piperazinyl]butoxy]-3,4-dihydrocarbostyril. The empirical formula is Carcinogenesis C..H..Cl.N.O. and its molecular weight is 448.38. The chemical structure is: 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). n addition, SD rats were dosed orally for 2 years at 10, 20, 40, and 6 maduloin, of native vere vose of any for years at ro, 2, 4, and and my/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 nammary gland adenocarcinomas and adenoacanth 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 12.1 Mechanism of Action

The mechanism of action of aripiprazole in schizophrenia or bipolar mania, increased at an oral dose of 60 mg/kg/day (19 times the MRHD).

An increase in mammary, pituitary, and endocrine pancreas neoplasms has peen found in rodents after chronic administration of other antipsychotic drugs and is considered to be mediated by prolonged dopamine D'-réceptor 12.2 Pharmacodynamics

Aripiprazole exhibits high affinity for dopamine D<sub>2</sub> and D<sub>3</sub>, serotonin 5-HT<sub>1A</sub> and 5-HT<sub>2A</sub> receptors (K, values of 0.34 nM, 0.8 nM, 1.7 nM, and 3.4 nM, respectively), moderate affinity for dopamine D<sub>4</sub>, serotonin 5-HT<sub>2A</sub> and 5-HT<sub>3</sub>, alpha<sub>1</sub>-adrenergic and histamine H<sub>1</sub> receptors (K, values of 44 nM, 15 nM, 39 nM, 57 nM, and 61 nM, respectively), and moderate affinity for the control of the

<u>Mutagenesis</u> chromosomal aberration assay in Chinese hamster lung (CHL) cells, the in vivo micronucleus assay in mice, and the unscheduled DNA synthesis assay in rats. Aripiprazole and a metabolite (2.3- DCPP) were clastogenic in 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. relevant to humans

Impairment of Fertility Female 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 seen at all doses, but no impairment of fertility was seen. Increased

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 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 mg/kg and 60 mg/kg. The 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 dehydrogenation, hydroxylation, and N-dealkylation. Based on *in vitro* studies, CYP3A4 and CYP2D6 enzymes are responsible for dehydrogenation and human risk is unknown mechanism have not been performed. The relevance of this finding to

[see Clinical Studies (14.1)] Four short-term monotherapy trials and one 6-week adjunctive trial in at endo adult patients and one short-term monotherapy trial in pediatric patients and one short-term monotherapy trial in pediatric patients (ages 10 to 17) with manic or mixed episodes [see Clinical Studies

response to antidepressant therapy during the current episode [see with or without psychotic features. Clinical Studies (14.3)]
Two short-term trials in pediatric patients (ages 6 to 17 years) for the

Tourette's disorder [see Clinical Studies (14.5)] 14.1 Schizophrenia

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 the reduction of the Y-MRS total score (Study 5 in Table 27) and CGI-BF 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 aripiprazole and the active comparators.

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 about the overall clinical state of the patient. In a 4-week trial (n=414) comparing two fixed doses of aripiprazole (15

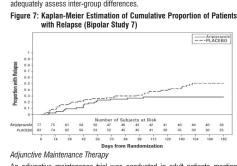
mg/day or 30 mg/day) to placebo, both doses of aripiprazole were superior to placebo in the PANSS total score (Study 1 in Table 26), PANSS positive subscale, and CGI-severity score. In addition, the 15 mg dose was superior to placebo in the PANSS negative subscale. In a 4-week trial (n=404) comparing two fixed doses of aripiprazole (20 mg/day 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 ariniprazole (10) mg/day, 15 mg/day, 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 negative subscale. In a 6-week trial (n=367) comparing three fixed doses of aripiprazole (2 mg/day, 5 mg/day, 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 mg and 5 mg doses did not demonstrate superiority to placebo on the primary outcome measure. Thus, the efficacy of 10 mg, 15 mg, 20 mg, and 30 mg daily doses was established in two studies for each dose. Among these doses, there was no

evidence that the higher dose groups offered any advantage over the lowest dose group of these studies. An examination of population subgroups did not reveal any clear evidence of differential responsiveness on the basis of age, gender, or race. A longer-term trial enrolled 310 inpatients or outpatients meeting DSM-IV criteria for schizophrenia who were, by history, symptomatically stable on other antipsychotic medications for periods of 3 months or longer. These patients were discontinued from their antipsychotic medications and andomized 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 er 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 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.

An examination of population subgroups did not reveal any clear evidence 14.5 Tourette's Disorder adequately assess inter-group differences.



92.7 (19.5) | -15.0 (2.38) | -12.7 (-19, -6.41) 93.2 (21.6) -11.7 (2.38) -9.4 (-15.71, -3.08 92.5 (20.9) -14.4 (2.45) -12.1 (-18.53, -5.68) 92.0 (12.6) -10.6 (1.93) -5.2 (-10.7, 0.19) 90 (11.9) -11.3 (1.88) -5.9 (-11.3, -0.58) 93.6 (15.7) | -26.7 (1.91) | -5.5 (-10.7, -0.21) 94 (16.1) -28.6 (1.92) -7.4 (-12.7, -2.13)

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

**Primary Efficacy Measure: PANSS** 

Change from Baseline (SE)

98.5 (17.2) -15.5 (2.4) -12.6 (-18.9. -6.2)

99 (19.2) -11.4 (2.39) -8.5 (-14.8, -2.1)

+ 94.2 (18.5) -13.9 (2.24) -9.0 (-14.8, -3.1)

90.7 (14.5) | -8.2 (1.9) | -2.9 (-8.29, 2.47)

100.2 (16.5) -2.9 (2.36)

94 3 (18 5) | -5.0 (2.17)

92.3 (21.8) -2.3 (2.35)

90.8 (13.3) | -5.3 (1.97)

94.6 (15.6) -21.2 (1.93)

SD: standard deviation; SE: standard error; LS Mean: least-squares

Study 2 | Aripiprazole (20 mg/day) + | 92.6 (19.5) | -14.5 (2.23) | -9.6 (-15.4, -3.8)

Placebo

Placebo

Placebo

Placebo

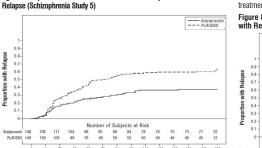
(30 mg/day)

nean; CI: unadjusted confidence interval.

Placebo

Study 4 Aripiprazole (2 mg/day)

LS Mean Placebo-



Acute 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

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. and 44% of patients were on 15 mg/day at endpoint. In the two studies with a starting dose of 30 mg/day, 86% and 85% of patients were on 30 mg/day at endpoint.

(ages 10 to 17) with manic or mixed episodes [see Clinical Studies (14.2)]

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 maid that the stabilizer manical in adult patients with MDD who had an inadequate was provided in the treatment of manic or mixed episodes was established in a 6-week, placebo-controlled study (n=384) with a 2-week lead-in mood stabilizer monotherapy phase in adult patients whom ent DSM-IV criteria for bipolar I disorder. This study included patients with manic or mixed episodes and with the control of the con Patients were initiated on open-label lithium (0.6 mEg/L to 1 mEg/L) or

 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 improvement 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 improvenient on the Y-wins load score) to fluthum or valprolate 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 mEg/L to 1 mEg/L or 50 meg/mL to 125 mcg/mL. respectively) was superior to lithium or valproate with adjunctive placebo

active control group consisting of either risperidone (one trial) or haloperidol (two trials), but they were not designed to allow for a comparison of actions and the active comparators.

The efficacy of aripiprazole in the treatment of bipolar I disorder in pediatric. anipipi acute and the acute comparators.

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 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 to the target dose in 5 days in the 10 mg/day treatment arm, and in 13 days i the 30 mg/day treatment arm. Both doses of aripiprazole were superior t

(absent) to 7 (extreme); total PANSS scores range from 30 to 210. The Clinical Global Impression (CGI) assessment reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient.

Table 27: Bipolar Studies Primary Efficacy Measure: Y-MRS LS Mean Change from Subtracted Baseline (SE) Placebo-29.0 (5.9) -12.52 (1.05) -5.33 (-7.9, -2.76) Study 1 | (30 / 15 mg/ Pediatric Patients

27.8 (5.7) | -8.15 (1.23) | -4.8 (-7.8, -1.8) 29 1 (6 9) -3 35 (1 22) Placebo (15 mg/day to 28.5 (5.6) -12.64 (0.84) -3.63 (-5.75, -1.51) 28.9 (5.9) 9.01 (0.81) 28 (5.8) -11.98 (0.8) 28.3 (5.8) -9.7 (0.83) Placebo (15 or 30 mg/ day) † + Lithium /Valproate -2.62 (-4.29, -0.95) 23.2 (5.7) -13.31 (0.5) Placebo + Lithium/Valproate 23 (4.9) -10.7 (0.69) 29.8 (6.5) -14.2 (0.89) -5.99 (-8.49, -3.5) Aripiprazole (30 mg/day) † 29.5 (6.3) -16.5 (0.87) -8.26 (-10.7, -5.77) 30.7 (6.8) -8.2 (0.91) --

ted confidence interval. ence (drug minus placebo) in least-squares mean change from baseline.

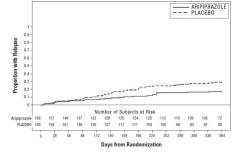
Maintenance Treatment of Bipolar I Disorder Monotherapy Maintenance Therapy A maintenance trial was conducted in adult patients meeting DSM-IV criteria for bipolar I disorder with a recent manic or mixed episode who had been stabilized on open-label aripiprazole and who had maintained a clinical response for at least 6 weeks. The first phase of this trial was an open-label 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 and in 11 days in the 30 mg/day at treatment arm. 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 control combined affective relapses (manic plus depressive), the primary outcom 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 th 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).

† Doses statistically significantly superior to placel

of differential responsiveness on the basis of age and gender; however, there were insufficient numbers of patients in each of the ethnic groups to

An adjunctive maintenance trial was conducted in adult patients meeting An adjunctive maintenance trial was conducted in aduit 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 mEq/L to 1.0 mEq/L) or valproate (50 mcg/mL to 125 mcg/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 ampiprazole with a starting dosa 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 andomized in a double-blind fashion, to either the same dose of ariningazole transition they were on at the end of the stabilization period or placebo plus lithium or valproate and were then monitored for manic, mixed, or depressive relapse for a maximum of 52 weeks. 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, o depressive episode, study discontinuation due to lack of efficacy accompanied by Y-MRS score > 16 and/or a MADRS > 16, or an SAE 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

an pipazole group (ry were leven than that in the placebo group (14) was similar to that in the placebo group (15). The Kaplan-Meier curves of the time from randomization to relapse to any mood event during the 52-week, double-blind treatment phase for aripiprazole and placebo groups are shown in Figure 8. Figure 8: Kaplan-Meier Estimation of Cumulative Proportion of Patients with Relapse to Any Mood Event (Bipolar Study 8)



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

Adults psychotic features and two of the studies also included patients with or The efficacy of aripiprazole in the adjunctive treatment of major depressive

disorder (MDD) was demonstrated in two short-term (6-week), placebo-controlled trials of adult patients meeting DSM-IV criteria for MDD who had had an inadequate response to prior antidepressant therapy (1 to 3 courses) in the current episode and who had also demonstrated an inadequate response to 8 weeks of prospective antidepressant therapy (paroxetine controlled-release, venlafaxine extended-release, fluoxetine CYP3A4 and CYP206 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 aripiprazole, the active metabolite, represents about 40% of aripiprazole, and N-dealkylation is catalyzed by CYP3A4. Aripiprazole is the predominant drug moiety in the systemic circulation. At strating dose of 30 mg/day in two studies and 15 mg/day once daily (with a starting dose of 30 mg/day in two studies and 15 mg/day once daily (with a starting dose of 30 mg/day in two studies and 15 mg/day once daily (with a starting dose of 30 mg/day in two studies and 15 mg/day once daily (with a starting dose of 30 mg/day in two studies and 15 mg/day once daily (with a starting dose of 30 mg/day in two studies and 15 mg/day once daily (with a starting dose of 15 mg/day. 48% of 6 weeks of antidepressant therapy at or above the minimal effective dose. escitalopram, or sertraline). Inadequate response for prospective treatmer was defined as less than 50% improvement on the 17-item version of the as less thall 30 a mighoration.

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

Store at 20° to 25°C (68° to 77°F); excursions permitted between 15° to 30°C (59° 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. reducing mean MADRS total scores (Studies 1, 2 in Table 28). In one study, aripiprazole was also superior to placebo in reducing the mean SDS score. In both trials, patients received aripiprazole adjunctive to antidepressants at

a dose of 5 mg/day, Based on tolerability and efficacy, doses could be adjusted by 5 mg increments, one week apart. Allowable doses were: 2 mg/day, 5 mg/day, 10 mg/day, 15 mg/day, and for patients who were not on Ingrody, 1 in Ingrody, 1 in Ingrody, 1 in Ingrody, and in patients with were not on potent CYP2D6 inhibitors (Incovertine and paroxetine, 20 mg/day, The mean final dose at the end point for the two trials was 10.7 mg/day and 11.4 mg/day.

Clinical Worsening of Depression and Suicide Risk Patients, their families, and their caregivers should be encouraged to be An examination of population subgroups did not reveal evidence of alert to the emergence of anxiety, agitation, panic attacks, insomnia, differential response based on age, choice of prospective antidepressant, or race. With regard to gender, a smaller mean reduction on the MADRS total

Study Number	Treatment Group	Primary Efficacy Measure: MADRS			
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo- subtracted Difference* (95% CI)	
Study 1	Aripiprazole (5 to 20 mg/ day) † + Antidepressant	25.2 (6.2)	-8.49 (0.66)	-2.84 (-4.53, -1.15)	
	Placebo + Antidepressan	27.0 (5.5)	-5.65 (0.64)		
Study 2	Aripiprazole (5 to 20 mg/ day) † + Antidepressant	26.0 (6.0)	-8.78 (0.63)	-3.01 (-4.66, -1.37)	
	Placebo + Antidepressan	26.0 (6.5)	-5.77 (0.67)		

nadjusted confidence interval.

Difference (drug minus placebo) in least-squares mean change from baseline.
Doses statistically significantly superior to placebo. 14.4 Irritability Associated with Autistic Disorder

The efficacy of aripiprazole in the treatment of irritability associated with autistic disorder was established in two 8-week, placebo-controlled trials in bediatric patients (6 to 17 years of age) who met the DSM-IV criteria for autistic disorder and demonstrated behaviors such as tantrums, aggression, self-injurious behavior, or a combination of these problems. Over 75% of these subjects were under 13 years of age. Efficacy was evaluated using two assessment scales: the Aberrant Behavior Checklist (ABC) and the Clinical Global Impression-Improvement (CGI-I) scale. The primary outcome measure in both trials was the change from baseline to endpoint in the Irritability subscale of the ABC (ABC-I). The ABC-I subscale measured 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 will adustic disporter (II=90), aged of to Tyears, received daily duses placebo or aripipirazole 2 mg/day to 15 mg/day hasped 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 or the ABC-I subscale compared with placebo. Table 29: Irritability Associated with Autistic Disorder Studies (Pediatric)

Study Number	Treatment Group	Primary Efficacy Measure: ABC-I			
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo- subtracted Difference* (95% CI)	
Study 1	Aripiprazole (2 to 15 mg/ day) †	29.6 (6.37)	-12.9 (1.44)	-7.9 (-11.7, -4.1	
	Placebo	30.2 (6.52)	-5.0 (1.43)		
Study 2	Aripiprazole (5 mg/day) †	28.6 (7.56)	-12.4 (1.36)	-4.0 (-7.7, -0.4)	
	Aripiprazole (10 mg/day) †	28.2 (7.36)	-13.2 (1.25)	-4.8 (-8.4, -1.3)	
	Aripiprazole (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)		
unadjusted * Differenc	ard deviation; SE: s confidence interval. e (drug minus place atistically significant	bo) in least-squ	ares mean chanç		

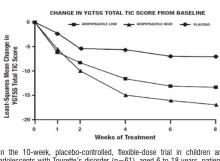
Pediatric Patients

he 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 age) who that the DSM-IV childral of Tourette's disorder and had a folial ric score (TTS) ≥ 20 to 22 on the Yale Global Tic Severity Scale (YGTSS). The YGTSS is a fully validated scale designed to measure current tic severity. Efficacy was evaluated using two assessment scales: 1) the Total Tic score (TTS) of the YGTSS and 2) the Clinical Global Impressions Scale for Tourette's Syndrome (CGI-TS), a clinician-determined summary measure that takes into account all available patient information. Over 65% of these natients were under 13 years of age. 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 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 after 2 days, with a subsequent increase to a target dose of 10 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 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 after 2 days with a subsequent for the first of the fi 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 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 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 in Figure 9.

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



In the 10-week, placebo-controlled, flexible-dose trial in children and adolescents with Tourette's disorder (n=61), aged 6 to 18 years, patients received daily doses of placebo or 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 rininrazole at the end of 10-week treatment was 6.54 mg/day. Table 30: Tourette's Disorder Studies (Pediatric)

Study Number	Treatment Group	Primary Efficacy Measure: YGTSS TTS			
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo- subtracted Difference* (95% CI)	
Study 1	Aripiprazole (low dose) †	29.2 (5.63)	-13.4 (1.59)	-6.3 (-10.2, -2.3	
	Aripiprazole (high dose) †	31.2 (6.4)	-16.9 (1.61)	-9.9 (-13.8, -5.9	
	Placebo	30.7 (5.95)	-7.1 (1.55)		
Study 2	Aripiprazole (2 to 20 mg/ day) †	28.3 (5.51)	-15 (1.51)	-5.3 (-9.8, -0.9)	
	Placebo	29.5 (5.6)	-9.6 (1.64)		

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

17 PATIENT COUNSELING INFORMATION

Discuss the following issues with patients prescribed aripiprazole:

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. 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 Micropas and Procurtions (5.2)). 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 ripiprazole 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. 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

a single agent for treatment of depression and has not been evaluated in pediatric maior depressive disorder. Pathological Gambling and Other Compulsive Behaviors 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 aripirazole. 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)].

questions they may have. It should be noted that aripiprazole is not approved as

Interference with Cognitive and Motor Performance Because aripiprazole 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

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 fructos **Pregnancy** 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

and feeding disorder) in a neonate. [see Use in Specific Populations (8.1)] Lactation azole use during pregnancy may affect milk supply. Advise the All philadore used using pregnancy may affect mine supply. Some analysis and 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)].

Manufactured by: Quagen Pharmaceuticals LLC West Caldwell, NJ 07006

Concomitant Medication

Rev.09/25

52032 ARIPIPRAZOLE Oral Solution (Quagen)\_02

NOV 19, 2025 01:00 PM



94 Country Line Rd, STE B, Colmar, PA 18915, Ph.:+1 267 768 8538 www.adiyapharma.com | info@adiyapharma.com

# **APPROVAL SHEET**

				Artwork No. : 251227	
Customer Name	:	Quagen Pharmaceut	icals LLC		
Customer Rep	: _	Mr. Naresh Chintalap	pati D	Pate Submitted : Nov 19, 2025	
		J	OB INFO		
Job Name	:	52032 ARIPIPRAZOI	E Oral Solution		
Туре	:	New Design 🗸	Reprint		
File Name	: 52032 ARIPIPRAZOLE Oral Solution (Quagen)				
Job Type	:	Outsert 🗸	Med Guide	Patient Guide	
Revision		09/25	Proof # : _ <b>07_N</b>	ov 19, 2025 01:00 PM	
Grain Direction	:	See the Artwork			
Manufacture by	•	Adiya Pharma	Manufacture for :	Quagen Pharmaceuticals LLC	
Font Size	:	6 pt	Flat Size	L 23.95" x W 20.1"	
			Final folded size :	1.5" x 3"	
Customer Item #	:	52032	Barcode Reader :	52032	
Paper Stock	:	27# Pharmopaque	Barcode Type :	Code 128	
Ink	•	Black			
			NOTES		
APPROVED: OK t	to	Print DATE:	Appro	oved By:	

<sup>\*</sup> Please review in detail for Layout, Content, Spelling, Spacing, Grammar, Structures, Colors, Barcode and all Specs related to his Artwork.

Adiya Pharma Inc. is not responsible for errors on printed products that appear on this proof.