

## Note: Position of the pharma code and product name will change as per the folding machine feasibility



Revised: 05/2025

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

Initial U.S. Approval: 2002

- WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS and SUICIDAL THOUGHTS AND BEHAVIORS WITH ANTIDEPRESSANT DRUGS See full prescribing information for complete boxed warning.
- Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Aripiprazole tablets are not approved for the treatment of patients with dementiarelated psychosis. (5.1)
- Increased risk of suicidal thinking and behavior in children, adolescents, and young adults takin antidepressants. Monitor for worsening and emergence of suicidal thoughts and behaviors. (5.3)

--RECENT MAJOR CHANGES Indications and Usage (1) 1/2025

1/2025

1/2025

1/2025

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# Warnings and Precautions Orthostatic Hypotension (5.8)

Seizures/Convulsions (5.11) Potential for Cognitive and Motor Impairment (5.12)

- -----INDICATIONS AND USAGE--
- Aripiprazole tablets are an atypical antipsychotic. Aripiprazole tablets are indicated for:
- Schizophrenia (14.1) Irritability Associated with Autistic Disorder (14.4)
- Treatment of Tourette's Disorder (14.5)

-----DOSAGE AND ADMINISTRATION-

#### Administer once daily without regard to meals (2)

		Initial Dose	Recommended Dose	Maximum Dose
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
Irritability associated with autistic disorder – pediatric patients (2.4)		2 mg/day	5 to 10 mg/day	15 mg/day
Tourstale Disorder (0.5)	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

- Known CYP2D6 poor metabolizers: Half of the usual dose (2.6)
- -- DOSAGE FORMS AND STRENGTHS-
- Tablets: 2 mg, 5 mg, 10 mg, 15 mg, 20 mg, and 30 mg (3)
- ---CONTRAINDICATIONS Known hypersensitivity to aripiprazole tablets (4)
- -----WARNINGS AND PRECAUTIONS-
- Cerebrovascular Adverse Reactions in Elderly Patients with Dementia-Related Psychosis: Increased incidence of cerebrovascular adverse reactions (e.g., stroke, transient ischemic attack, including fatalities) (5.1, 5.2) 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) o 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 antipsychotics (5.6)

FULL PRESCRIBING INFORMATION: CONTENTS\* WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS AND SUICIDAL THOUGHTS AND BEHAVIORS WITH ANTIDEPRESSANT DRUGS

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WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS and SUICIDAL THOUGHTS AND BEHAVIORS WITH ANTIDEPRESSANT DRUGS Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Aripiprazole tablets are not approved for the treatment of patients with dementia-related psychosis *(see Warnings and Precautions (5,1))*.

Weight Gain: Weight gain has been observed with atypical antipsychotic use. Monitor weight (5.6) Pathological Gambling and Other Compulsive Behaviors: Consider dose reduction or discontinua ation (5.7)

Orthostatic Hypotension: Monitor heart rate and blood pressure and warn patients with known cardiovascular or cerebrovascular disease, and risk of dehydration or syncope (5.8) Leukopenia, Neutropenia, and Agranulocytosis: have been reported with antipsychotics including aripiprazole tablets. Patients with a history of a clinically significant low white blood cell count (WBC) or a drug-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of aripiprazole tablets should be considered at the first sign of a

clinically significant decline in WBC in the absence of other causative factors (5.10) Seizures/Convulsions: Use cautiously in patients with a history of seizures or with conditions that lower the seizure 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. Closely supervise high-risk patients

(5.14)-- ADVERSEREACTIONS-

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

Pediatric patients (6 to 17 years) with autistic disorder: sedation, fatigue, vomiting, somnolence, tremor,

Perkaia, drooling, decreased appetite, salivary hypersecretion, extrapyramidal disorder, and lethargy Pediatric patients (6 to 18 years) with Tourette's Disorder: sedation, somnolence, nausea, headache,

#### nasopharyngitis, fatigue, increased appetite To report SUSPECTED ADVERSE REACTIONS, contact Hetero Labs Limited at 1-866-495-1995 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

--DRUGINTERACTIONS--Dosage adjustment due to drug interactions (7.1)

Factors	Dosage Adjustments for Aripiprazole Tablets
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)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

#### Fasting LDL Cholesterol Aripiprazole Tablets 2/332 0.6 Normal to High <100 mg/dL to ≥160 2/268 0.7 Placebo ng/dL) HDL Cholesterol Aripiprazole Tablets 121/1.066 11.4 rmal to Lov (≥40 mg/dL to <40 99/794 12.5 Placebo mg/dL)

In monotherapy trials in adults, the proportion of patients at 12 weeks and 24 weeks with changes from Normal to High in total cholesterol (fasting/nonfasting), fasting triglycerides, and fasting LDL cholesterol were similar between aripiprazole- and placebo-treated patients: at 12 weeks, Total Cholesterol (fasting/nonfasting), 1/71 (1.4%) vs. 3/74 (4.1%); Fasting Triglycerides, 8/62 (12.9%) vs. 5/37 (13.5%); Fasting LDL Cholesterol, 0/34 (0%) vs. 1/25 (4 %), respectively; and at 24 weeks. Total Cholesterol (fasting/nonfasting), 1/42 (2.4%) vs. 3/37 (8.1%); Fasting Triglycerides, 5/34 (14.7%) vs. 5/20 (25%); Fasting LDL Cholesterol, 0/22 (0%) vs. 1/18 (5.6%), respectively.

#### Pediatric Patients and Adolescents

Table 9 shows the proportion of adolescents with schizophrenia (13 to 17 years) and pediatric patients with another indication (10 to 17 years) with changes in total cholesterol and HDL cholesterol (pooled from two placebo-controlled trials; median exposure 42 to 43 days) and fasting triglycerides (pooled from two placebo-controlled trials; median exposure 42 to 44 days).

Table 9: Changes in Blood Lipid Parameters from Placebo-Controlled Monotherapy Trials in Pediatric and

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

monotherapy trials of adolescents with schizophrenia and pediatric patients with another indication the proportion of patients at 12 weeks and 24 weeks with changes from Normal to High in total cholesterol (fasting/nonfasting), fasting triglycerides, and fasting LDL cholesterol were similar between aripiprazole- and placebo-treated patients: at 12 weeks, Total Cholesterol (fasting/nonfasting), 0/57 (0%) vs. 0/15 (0%); Fasting Triglycerides, 2/72 (2.8%) vs. 1/14 (7.1%), respectively; and at 24 weeks, Total Cholesterol (fisting, 0/36 (0%) vs. 0/12 (0%); Fasting Triglycerides, 1/47 (2.1%) vs. 1/10 (10 %), respectively.

Table 10 shows the proportion of patients with changes in total cholesterol (fasting/nonfasting) and fasting triglycerides (median exposure 56 days) and HDL cholesterol (median exposure 55 to 56 days) from two placebo-controlled trials in pediatric patients (6 to 17 years) with irritability associated with autistic disorder.

Table 10: Changes in Blood Lipid Parameters from Placebo-Controlled Trials in Pediatric Patients with Autistic Disorde

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

Table 11 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 11: Changes in Blood Lipid Parameters from Placebo-Controlled Trials in Pediatric Patients with

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

Weight Gair Neight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recom

Adults

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

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 adjunctive placebo.

Table 12 shows the percentage of adult patients with weight gain  $\geq$ 7% of body weight by indication

Table 12: Percentage of Patients from Placebo-Controlled Trials in Adult Patients with Weight Gain ≥7% of

Placebo

Body Weight					
	Indication	Treatment Arm	N	Patients n (%)	
	Schizophrenia*	Aripiprazole Tablets	852	69 (8.1)	
ght gain ≥ 7%	Schizophrenia	Placebo	379	12 (3.2)	
ody weight		Aripiprazole Tablets	719	16 (2.2)	

598

16 (2.7)

#### Less Common Adverse Reactions in Adults

Preferred Term

Eye Disorders

Nausea

Constipation

Vomiting

Dvspepsia

Dry Mouth

Toothache

Fatigue

Myalgia

Headache

Dizziness

Akathisia

Sedation

Tremor

Agitation

Insomnia

Anxiety

Cough

Restlessness

Pharyngolaryngeal Pain

Somnolence

Psychiatric Disorders

Pain

Abdominal Discomfor

Stomach Discomfort

Musculoskeletal Stiffness

**Nervous System Disorders** 

Extrapyramidal Disorder

Pain in Extremity

Muscle Spasms

General Disorders and Administration Site Conditions

Musculoskeletal and Connective Tissue Disorders

Respiratory, Thoracic, and Mediastinal Disorders

had an incidence equal to or less than placebo.

Pediatric Patients (13 to 17 years) with Schizophrenia

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

extrapyramidal disorder, somnolence, and tremor,

Pediatric Patients (6 to 17 years) with Autistic Disorder

Commonly Observed Adverse Reactions

administered in doses of 2 to 15 mg/day.

Commonly Observed Adverse Reactions

Preferred Term

Sedation

Fatique

remor

Pyrexia 1

Drooling

Lethargy

Table 19

Preferred Term

omnolence

Nasopharyngitis

Increased Appetite

Preferred Term

Eye Disorders

Vomiting

Nausea

Diarrhea

Fatigue

Pyrexia

Irritability

Asthenia

Nasopharyngitis

Weight Increased

Increased Appetite

Decreased Appetite

Muscle Rigidity

Somnolence

Headache

Sedation Tremor

Akathisia

Drooling

Lethargy

Dizziness

Dystonia

Epistaxis

Rash

Schizophrenia

Musculoskeletal Stiffness

Nervous System Disorders

Extrapyramidal Disorder

Investigations

Blurred Visior

Gastrointestinal Disorders

Abdominal Discomfort

Salivary Hypersecretion

Abdominal Pain Upper

nfections and Infestations

Metabolism and Nutrition Disorders

Musculoskeletal and Connective Tissue Disorders

Respiratory, Thoracic, and Mediastinal Disorders

which had an incidence equal to or less than placebo.

tremor (incidences were placebo, 2%; 10 mg, 2%; 30 mg, 11.8%).

Skin and Subcutaneous Tissue Disorders

**General Disorders and Administration Site Conditions** 

ourette's Disorder, or Other Indication

Sedation

Vausea

Fatigue

leadache

Decreased Appetite

Salivary Hypersecretion

Extrapyramidal Disorder

Pediatric Patients (6 to 18 years) with Tourette's Disorder

Commonly Observed Adverse Reactions

Adverse Reactions Associated with Discontinuation of Treatment

aripiprazole and treated with placebo was 7% and 1%, respectively.

niting

Somnolence

Adverse Reactions Associated with Discontinuation of Treatment

aripiprazole and treated with placebo was 5% and 2%, respectively.

Adverse Reactions Associated with Discontinuation of Treatment

aripiprazole and treated with placebo was 10% and 8%, respectively.

Blurred Vision

astrointestinal Disorders

Table 15 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 another indication), including only those reactions that occurred in 2% or more of patients treated with aripiprazole (doses  $\geq 2 \text{ mg/day}$ ) and for which the incidence in patients treated with aripiprazole was greater than the incidence in patients treated with placebo in the combined dataset

Aripiprazole Tablets

( n=1,843)

15

11

4

10

10

5

19

18

17

3

Adverse reactions reported by at least 2% of patients treated with aripiprazole, except adverse reactions which

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

The following findings are based on one 6-week, placebo-controlled trial in which oral aripiprazole was

The incidence of discontinuation due to adverse reactions between pediatric patients (13 to 17 years) treated with

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

The following findings are based on two 8-week, placebo-controlled trials in which oral aripiprazole was

The incidence of discontinuation due to adverse reactions between pediatric patients (6 to 17 years) treated with

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

**Aripiprazole Tablets** 

(n=212)

17

10

10

9

6

The following findings are based on one 8-week and one 10-week, placebo-controlled trials in which oral aripiprazole was administered in doses of 2 to 20 mg/day.

The incidence of discontinuation due to adverse reactions between pediatric patients (6 to 18 years) treated with

Disorder (incidence of 5% or greater and aripiprazole incidence at least twice that for placebo) are shown in

Aripiprazole Tablets

(n=121)

13

11

10

Less Common Adverse Reactions in Pediatric Patients (6 to 18 years) with Schizophrenia, Autistic Disorder

Table 20 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 one indication, 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 22 mg/day) and for which the incidence in patients treated

Table 20: Adverse Reactions in Short-Term, Placebo-Controlled Trials of Pediatric Patients (6 to 18 years) Treated with Aripiprazole Tablets

Aripiprazole Tablets

(n=732)

Δ

3

10

16

12

6

3

with aripiprazole was greater than the incidence in patients treated with placebo.

Table 19: Commonly Observed Adverse Reactions in Short-Term, Placebo-Controlled Trials of Pediatric

Patients (6 to 18 years) with Tourette's Disorder Treated with Aripiprazole

monly observed adverse reactions associated with the use of aripiprazole in pediatric patients with Tourette's

Percentage of Patients Reporting Reaction

Percentage of Patients Reporting Reaction

Percentage of Patients Reporting Reaction

Placebo

(n=101)

2

0

0

0

(n=72)

6

4

0

0

Placebo

(n=370)

0

3

2

2

2

3

4

10

4

0

2

Table 18: Commonly Observed Adverse Reactions in Short-Term, Placebo-Controlled Trials of Pediatric Patients (6 to 17 years) with Autistic Disorder Treated with Aripiprazole

Percentage of Patients Reporting Reaction

Placebo

(n=1,166

1

11

Δ

2

2

2

23

4

3

3

17

13

13

3

#### Table 15: Adverse Reactions in Short-Term, Placebo-Controlled Trials in Adult Patients Treated with Aripiprazole Tablets

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 years; there was a reduction in risk with antidepressant use in patients aged 65 years 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)].* 

## INDICATIONS AND USAGE

- Aripiprazole tablets are indicated for the treatment of
- Schizophrenia
- Irritability Associated with Autistic Disorder
- Treatment of Tourette's Disorder
- 2 DOSAGE AND ADMINISTRATION
- 2.1 Schizophrenia

#### Adults

The recommended starting and target dose for aripiprazole tablets is 10 or 15 mg/day administered on a once-aday schedule without regard to meals. Aripiprazole tablets have 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 Studies (14.1)].

Maintenance Treatment: Maintenance of efficacy in schizophrenia was demonstrated in a trial involving patients with schizophrenia who had been symptomatically stable on other antipsycholic medications for periods of 3 months or longer. These patients were discontinued from those medications and randomized to either aripiprazole tablets 15 mg/day or placebo and observed for relapse [see Clinical Studies (14.1)]. Patients should be periodically reassessed to determine the continued need for maintenance treatment

#### Adolescents

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

#### Switching from Other Antipsychotics

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

#### 2.4 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 one week [see Clinical Studies (14.4)]. Patients should be periodically reassessed to determine the continued need for maintenance treatment.

## 2.5 Tourette's Disorder

#### Pediatric Patients (6 to 18 years)

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

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

For patients weighing 50 kg or more, dosing should be initiated at 2 mg/day for 2 days, and then increased to 5 mg/day for 5 days, with a target dose of 10 mg/day on Day 8. The dose can be increased up to 20 mg/day for patients who do not achieve optimal control of tics. Dosage adjustments should occur gradually in increments of 5 mg/day at intervals of no less than one week [see Clinical Studies (14.5)].

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

2.6 Dosage Adjustments for Cytochrome P450 Considerations Dosage adjustments are recommended in patients who are known CYP2D6 poor metabolizers and in patients taking concomitant CYP3A4 inhibitors or CYP2D6 inhibitors or strong CYP3A4 inducers (see Table 1). When the cadministered drug is withdrawn from the combination therapy, aripipracid dosage should then be adjusted to its original level. When the coadministered CYP3A4 inducer is withdrawn, aripiprazole 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 1: Dose Adjustments for Aripiprazole in Patients who are known CYP2D6 Poor Metabolizers and Patients Taking Concomitant CYP2D6 Inhibitors, CYP3A4 Inhibitors, and/or CYP3A4 Inducers

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

#### 3 DOSAGE FORMS AND STRENGTHS

Aripiprazole tablets, USP are available as described in Table 2.

#### Table 2: Aripiprazole Tablets Presentations

Tablet Strength	Tablet Color/Shape	Tablet Markings
2 mg	Light green to green modified rectangle	"I" and "94"
5 mg	Light blue to blue modified rectangle	"I" and "95"
10 mg	Light pink to pink modified rectangle	"I" and "96"
15 mg	Light yellow to yellow round	"I" and "97"
20 mg	White to off white round	"I" and "98"
30 mg	Light pink to pink	"I " and "99"

#### 4 CONTRAINDICATIONS

Aripiprazole tablets are contraindicated in patients with a history of a hypersensitivity reaction to aripiprazole. Reactions have ranged from pruritus/urticaria to anaphylaxis [see Adverse Reactions (6.2)]. 5 WARNINGS AND PRECAUTIONS

#### 5.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

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

# Boxed Warn

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

In three, 10-week, placebo-controlled studies of aripiprazole tablets 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  $\geq$ 3% and aripiprazole tablets incidence at least twice that for placebo were lethargy [placebo 2%, aripiprazole tablets 5%], somnolence (including sedation) [placebo 3%, aripiprazole tablets 8%]. and incontinence (primarily, urinary incontinence) [placebo 1%, aripiprazole tablets 5%], excessive salivation

should be given to changing the therapeutic cluding possibly dis medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggre

impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and

pediatric patients being treated with antidepressants for MDD as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening

of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

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

It should be noted that aripiprazole is not approved for use in treating depression in the pediatric population. 5.4 Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) may occur with administration of antipsychotic drugs, including aripiprazole. Rare cases of NMS occurred during aripiprazole treatment in the worldwide clinical database. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, oglobinuria (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 (CNS) pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

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

#### 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 nent, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient ncrease. 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 longterm 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. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

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

# 5.6 Metabolic Changes

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

#### Hyperglycemia/Diabetes Mellitus

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

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

#### Adults

exposure 57 days).

In an analysis of 13, placebo-controlled, monotherapy trials in adults, primarily with schizophrenia or another indication, the mean change in fasting glucose in aripiprazole-treated patients (+4.4 mg/dL; median exposure 25 days; N=1,057) was not significantly different than in placebo-treated patients (+2.5 mg/dL; median exposure 22 days; N=799). Table 4 shows the proportion of aripiprazole-treated patients with normal and borderline fasting glucose at baseline (median exposure 25 days) that had treatment-emergent high fasting glucose measurements ompared to placebo-treated patients (median exposure 22 days).

#### Table 4: Changes in Fasting Glucose from Placebo-Controlled Monotherapy Trials in Adult Patients

	Category Change (at least once) from Baseline	Treatment Arm	n/N	%
	Normal to High (<100 mg/dL to ≥126 mg/dL)	Aripiprazole Tablets	31/822	3.8
Fasting Olyapos		Placebo	22/605	3.6
Fasting Glucose	Borderline to High (≥100 mg/dL and <126 mg/dL to	Aripiprazole Tablets	31/176	17.6
	≥126 mg/dL)	Placebo	13/142	9.2

At 24 weeks, the mean change in fasting glucose in aripiprazole-treated patients was not significantly different than in placebo-treated patients [+2.2 mg/dL (n=42) and +9.6 mg/dL (n=28), respectively].

Pediatric Patients and Adolescents

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

In an analysis of two placebo-controlled trials in pediatric and adolescent patients with irritability associated with autistic disorder (6 to 17 years) with median exposure of 56 days, the mean change in fasting glucose in aripiprazole-treated patients (-0.2 mg/dL; N=83) was not significantly different than in placebo-treated patients (-0.6 mg/dL; N=33).

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

Table 6 shows the proportion of patients with changes in fasting glucose levels from the pooled adolescent schizophrenia and another indication (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

#### Table 6: Changes in Fasting Glucose from Placebo-Controlled Trials in Pediatric and Adolescent Patients

4 to 6 weeks duratior	1

another indication<sup>†</sup>

#### <sup>†</sup>3 weeks duration Pediatric Patients and Adolescents

Wei

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

In two, short-term, placebo-controlled trials in patients (6 to 17 years) with irritability associated with autistic der 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. In two, short-term, placebo-controlled trials in patients (6 to 18 years) with Tourette's Disorder with median

exposure of 57 days, the mean change in body weight in aripiprazole-treated patients was +1.5 kg (n=105) compared to +0.4 kg (n=66) in placebo-treated patients. Table 13 shows the percentage of pediatric and adolescent patients with weight gain  $\geq$ 7% of body weight by

Table 13: Percentage of Patients from Placebo-Controlled Monotherapy Trials in Pediatric and Adolescent

#### Patients with Weight Gain ≥7% of Body Weight

	Indication	Treatment Arm	N	Patients n (%)
	Pooled Schizophrenia and another indication*	Aripiprazole Tablets	381	20 (5.2)
		Placebo	187	3 (1.6)
Weight gain ≥7%	Irritability	Aripiprazole Tablets	209	55 (26.3)
of body weight	Associated with Autistic Disorder <sup>†</sup>	Placebo	98	7 (7.1)
	Tourette's	Aripiprazole Tablets	105	21 (20.0)
	Disorder <sup>‡</sup>	Placebo	66	5 (7.6)

#### \*4 to 6 weeks duration <sup>†</sup>8 weeks duration

#### <sup>‡</sup>8 to 10 weeks duration

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

In an open-label trial that enrolled patients from two short-term, placebo-controlled trials, patients (6 to 17 years) with irritability associated with autistic disorder, as well as de novo patients, 60.3% (199/330) completed one year of therapy with 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

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

#### 5.8 Orthostatic Hypotension

Aripiprazole may cause orthostatic hypotension, perhaps due to its alpha1-adrenergic receptor antagonism. The incidence of orthostatic hypotension-associated events from short-term, placebo-controlled trials of adult patients no oral aripiprazole (n=2.47) included (aripiprazole incidence, placebo encidence) orthostatic hypotension (1%, 0.3%), postural dizziness (0.5%, 0.3%), and syncope (0.5%, 0.4%); of pediatric patients 6 to 18 years of age n=732) on oral aripiprazole included orthostatic hypotension (0.5%, 0%), postural dizziness (0.4%, 0%), and cope (0.2%, 0%) [see Adverse Reactions (6.1)].

The incidence of a significant orthostatic change in blood pressure (defined as a decrease in systolic blood pressure  $\geq$ 20 mmHg accompanied by an increase in heart rate  $\geq$ 25 bpm when comparing standing to supine values) for aripiprazole was not meaningfully different from placebo (aripiprazole incidence, placebo incidence): 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 or conduction abnormalities), cerebrovascular disease, or conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications) [see Drug Interactions (7.1)].

#### 5.9 Falls

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

#### 5.10 Leukopenia, Neutropenia, and Agranulocytosis

In clinical trials and/or postmarketing experience, events of leukopenia and neutropenia have been reported temporally related to antipsychotic agents, including aripiprazole. Agranulocytosis has also been reported. Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC)/absolute clinically significant low WBC/ANC or drug-induced leukopenia/neutropenia, perform a complete blood count

(CBC) frequently during the first few months of therapy. In such patients, consider discontinuation of aripiprazole at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Monitor patients with clinically significant neutropenia for fever or other symptoms or signs of infection and treat promptly if such symptoms or signs occur. Discontinue aripiprazole in patients with severe neutropenia (absolute neutrophil count <1.000/mm<sup>3</sup>) and follow their WBC counts until recovery.

#### 5.11 Seizures/Convulsions

prevalent in a population of 65 years or older.

5.12 Potential for Cognitive and Motor Impairment

aripiprazole in short-term, placebo-controlled trials.

therapy with aripiprazole does not affect them adversely.

5.13 Body Temperature Regulation

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

As with other antipsychotic drugs, aripiprazole should be used cautiously in patients with a history of seizures or with conditions that lower the seizure threshold. Conditions that lower the seizure threshold may be more

Aripiprazole, like other antipsychotics, may have the potential to impair judgment, thinking, or motor skills. For example, in short-term, placebo-controlled trials, somnolence (including sedation) was reported as follows

(aripiprazole incidence, placebo incidence); in adult patients (n=2,467) treated with oral aripiprazole (11%,

discontinuation in 0.3% (8/2,467) of adult patients and 3% (20/732) of pediatric patients (6 to 18 years) on oral

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

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

Appropriate care is advised when prescribing aripiprazole for patients who will be experiencing conditions which

may contribute to an elevation in core body temperature, (e.g., exercising strenuously, exposure to extreme heat,

receiving concomitant medication with anticholinergic activity, or being subject to dehydration) [see Adverse

The possibility of a suicide attempt is inherent in psychotic illnesses 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%) and in pediatric patients ages 6 to 17 years (n=611; 24%, 6%). Somnolence (including

bo 0%, aripiprazole tablets 4%], and lightheadedness [placebo 1%, aripiprazole tablets 4%].

The safety and efficacy of aripiprazole in the treatment of patients with psychosis associated with dementia have not been established. If the prescriber elects to treat such patients with aripiprazole, assess for the emergence of difficulty swallowing or excessive somnolence, which could predispose to accidental injury or aspiration [see Boxed Warning].

#### 5.2 Cerebrovascular Adverse Events, Including Stroke

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

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

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist 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 years) with MDD and other spychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24 years; there was a reduction with antidepressants compared to placebo in adults aged 65 years and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, Obsessive Compulsive Disorder (CCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1,000 patients treated) are provided in Table 3.

#### Table 3:

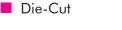
Drug-Placebo Difference in Number of Cases of Suicidality Age Range per 1000 Patients Treated Increases Compared to Placebo <18 14 additional cases 18 to 24 5 additional cases Decreases Compared to Placebo 25 to 64 1 fewer case 6 fewer cases ≥65

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not icient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

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

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

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

Dyslipidemia

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

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

#### Adults

Table 7 shows the proportion of adult patients, primarily from pooled, schizophrenia and another indication monotherapy, placebo-controlled trials, with changes in total cholesterol (pooled from 17 trials; median exposure 21 to 25 days), fasting triglycerides (pooled from eight trials; median exposure 42 days), fasting LDL cholesterol (pooled from eight trials; median exposure 39 to 45 days, except for placebo-treated patients with baseline normal fasting LDL measurements, who had median treatment exposure of 24 days) and HDL cholesterol (pooled from nine trials; median exposure 40 to 42 days).

#### Table 7: Changes in Blood Lipid Parameters from Placebo-Controlled Monotherapy Trials in Adults

	Treatment Arm	n/N	%
Total Cholesterol	Aripiprazole Tablets	34/1,357	2.5
Normal to High $(<200 \text{ mg/dL to } \ge 240 \text{ mg/dL})$	Placebo	27/973	2.8
Fasting Triglycerides	Aripiprazole Tablets	40/539	7.4
Normal to High $(<150 \text{ mg/dL to } \ge 200 \text{ mg/dL})$	Placebo	30/431	7

#### 5.15 Dysphagia

Reactions (6.2)].

5.14 Suicide

6.2)].

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

#### 6 ADVERSE REACTIONS

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

- Increased Mortality in Elderly Patients with Dementia-Related Psychosis [see Boxed Warning and Warnings and Precautions (5.1)]
- Cerebrovascular Adverse Events, Including Stroke [see Warnings and Precautions (5.2)]
- Suicidal Thoughts and Behaviors in Children, Adolescents, and Young Adults [see Boxed Warning and Warnings and Precautions (5.3)]
- Neuroleptic Malignant Syndrome (NMS) [see Warnings and Precautions (5.4)] Tardive Dyskinesia [see Warnings and Precautions (5.5)] Metabolic Changes [see Warnings and Precautions (5.6)]

- Pathological Gambling and Other Compulsive Behaviors [see Warnings and Precautions (5.7)] Orthostatic Hypotension [see Warnings and Precautions (5.8)]
- Falls [see Warnings and Precautions (5.9)]

- Fails (see Warnings and Precautions (5.9)) Leukopenia, Neutropenia, and Agranulocytosis [see Warnings and Precautions (5.10)] Seizures/Convulsions [see Warnings and Precautions (5.11)] Potential for Cognitive and Motor Impairment [see Warnings and Precautions (5.12)] Body Temperature Regulation [see Warnings and Precautions (5.13)] Suicide [see Warnings and Precautions (5.14)]

- Dysphagia [see Warnings and Precautions (5,15)]

#### 6.1 Clinical Trials Experience

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

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

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, another indications, dementia of the Alzheimer's type, Parkinson's disease, and alcoholism, and who had approximately 7,619 patient-years of exposure to oral aripiprazole and 749 patients with exposure to aripiprazole injection. A total of 3,390 patients were treated with oral aripiprazole for at least 180 days and 1,933 patients treated with oral aripiprazole had at least one year of exposure

Aripiprazole has been evaluated for safety in 1,686 pediatric patients (6 to 18 years) who participated in multiple dose, clinical trials in schizophrenia, another indication, autistic disorder, or Tourette's Disorder and who had approximately 1,342 patient-years of exposure to oral aripiprazole. A total of 959 pediatric patients were treated with oral aripiprazole for at least 180 days and 556 pediatric patients treated with oral aripiprazole had at least one vear of exposure.

The conditions and duration of treatment with aripiprazole (monotherapy and adjunctive therapy with noncomparative open-label studies, inpatient and outpatient studies, fixed- and flexible-dose studies, and shortand longer-term exposure.

#### Adult Patients with Schizophrenia

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

#### Commonly Observed Adverse Reactions

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

#### Autistic Disorder

30 mg, was somnolence [in mg, 7.5%; 30 mg, 12.6%].

Dose-Related Adverse Reactions

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

Adverse reactions reported by at least 2% of pediatric patients treated with aripiprazole, except adverse reactions

Dose response relationships for the incidence of treatment-emergent adverse events were evaluated from four trials in adult patients with schizophrenia comparing various fixed doses (2, 5, 10, 15, 20, and 30 mg/day) of oral aripiprazole to placebo. This analysis, stratified by study, indicated that the only

adverse reaction to have a possible dose response relationship, and then most prominent only with 30 mg, was somnolence [including sedation]; (incidences were placebo, 7.1%; 10 mg, 8.5%; 15 mg, 8.7%; 20

In the study of pediatric patients (13 to 17 years of age) with schizophrenia, three common adverse reactions appeared to have a possible dose response relationship: extrapyramidal disorder (incidences were placebo, 5%; 10 mg, 13%; 30 mg, 21.6%); sommolence (incidences were placebo, 6%; 10 mg, 11%; 30 mg, 21.6%); and

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 relations

Extrapyramidal Symptoms

Schizophrenia

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

Objectively collected data from those trials was collected for EPS using the Simpson Angus Scale (SAS), for akathisia using the Barnes Akathisia Rating Scale (BARS), and for dyskinesias using the Assessments of Involuntary Movement Scales (AIMS). In the adult schizophrenia trials, the objectively collected data did not show a difference between aripiprazole and placebo, with the exception of the BARS (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 SAS (aripiprazole, 0.24; placebo, -0.29).

Similarly, in a long-term (26 week), placebo-controlled trial of schizophrenia in adults, objectively collected data for EPS using the SAS, for akathisia using the BARS, and for dyskinesias using the AIMS did not show a difference between aripiprazole and placebo.

Autistic Disorder

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

In the pediatric (6 to 17 years) short-term autistic disorder trials, the SAS showed a significant difference between aripiprazole and placebo (aripiprazole, 0.1; placebo, -0.4). Changes in the BARS and the AIMS 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 patients was 4% vs. 6% for placebo.

the pediatric (6 to 18 years) short-term Tourette's Disorder trials, changes in the SAS, BARS and AIMS were not clinically meaningfully different for aripiprazole and placebo

Dystonia

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

Additional Findings Observed in Clinical Trials

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

The adverse reactions reported in a 26-week, double-blind trial comparing oral aripiprazole tablets 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 tablets 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 weeks), active-controlled study, the incidence of tremor was 5% (40/859) for aripiprazole.

# 

#### Other Adverse Reactions Observed During the Premarketing Evaluation of Aripiprazole

The following listing does not include reactions: 1) already listed in previous tables or elsewhere in labeling, 2) for which a drug cause was remote, 3) which were so general as to be uninformative, 4) which were not considered to have significant clinical implications, or 5) which occurred at a rate equal to or less than placebo. Reactions are categorized by body system according to the following definitions: frequent adverse reactions are those occurring in at least 1/100 patients: infrequent adverse reactions are those occurring in 1/100 to 1/1,000 patients; rare reactions are those occurring in fewer than 1/1,000 patients:

Adults

- Blood and Lymphatic System Disorders: rare thrombocytopenia *Cardiac Disorders: infrequent –* bradycardia, palpitations, *rare* – atrial flutter, cardio-respiratory arrest, atrioventricular block, atrial fibrillation, angina pectoris, myocardial ischemia, myocardial infarction,
- cardiopulmonary failure Eye Disorders: infrequent – photophobia; rare - diplopia
- Gastrointestinal Disorders: infrequent gastroesophageal reflux disease
- General Disorders and Administration Site Conditions: frequent asthenia; infrequent peripheral 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: frequent - blood prolactin decreased, weight decreased, infrequent - hepatic enzyme increased, blood glucose increased, blood lactate dehydrogenase increased, gamma glutamyl transferase increased; rare – blood prolactin increased, blood urea increased, blood creatinine increased, blood bilirubin increased, electrocardiogram QT prolonged, glycosylated hemoglobin increased Metabolism and Nutrition Disorders: frequent - anorexia; rare - hypokalemia, hyponatremia,
- hypoglycemia Musculoskeletal and Connective Tissue Disorders: infrequent - muscular weakness, muscle tightness;
- rare rhabdomyolysis, mobility decreased Nervous System Disorders: infrequent parkinsonism, memory impairment, cogwheel rigidity,
- hypokinesia, bradykinesia; rare akinesia, myoclonus, coordination abnormal, speech disorder, Grand Mal convulsion, Automatical and a state of the s
- anorgasmia, tic, homicidal ideation, catatonia, sleepwalking
- Renal and Urinary Disorders: rare urinary retention, nocturia Reproductive System and Breast Disorders: infrequent erectile dysfunction; rare gynecomastia, menstruation irregular, amenorrhea, breast pain, priapism
- Respiratory, Thoracic, and Mediastina Disorders: infrequent nasal congestion, dyspnea Skin and Subcutaneous Tissue Disorders: infrequent rash, hyperhidrosis, pruritus, photosensitivity reaction, alopecia; rare - urticaria

Vascular Disorders: infrequent – hypotension, hypertension

#### Pediatric Patients

Most adverse events observed in the pooled database of 1.686 pediatric patients, aged 6 to 18 years, were also observed in the adult population. Additional adverse reactions observed in the pediatric population are listed below

- Eve Disorders: infrequent oculogyric crisis
- Gastrointestinal Disorders: infrequent tongue dry, tongue spasm
- Investigations: frequent blood insulin increased
- Nervous System Disorders: infrequent sleep talking
- Renal and Urinary Disorders: frequent enuresis Skin and Subcutaneous Tissue Disorders: infrequent - hirsutisi

#### 6.2 Postmarketing Experience

The following adverse reactions have been identified during postanproval use of ariniprazole. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure: occurrences of allergic reaction (anaphylactic reaction, angioedema, laryngospasm, pruritus/uticaria, or oropharyngeal spasm), blood glucose fluctuation, drug reaction with eosinophilia and systemic symptoms (DRESS), hiccups, oculogyric crisis, pathological

#### gambling, and fecal incontinence. 7 DRUG INTERACTIONS

## 7.1 Drugs Having Clinically Important Interactions with Aripiprazole

# Table 22: Clinically Important Drug Interactions with Aripiprazole:

Concorr	Class	Clinical Rationale	Clinical Recommendation
itracona strong C	YP3A4 Inhibitors (e.g., zole, clarithromycin) or YP2D6 inhibitors (e.g., e, fluoxetine, paroxetine)	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)].	Reduce the aripiprazole dosage when administered concomitantly with a strong CYP3A4 inhibitor or a strong CYP2D6 inhibitor [see Dosage and Administration (2.6)].
	YP3A4 Inducers (e.g., izepine, rifampin)	Concomitant use of aripiprazole and carbamazepine decreased the exposure of aripiprazole compared to the use of aripiprazole alone [see Clinical Pharmacology (12.3)].	Increase the aripiprazole dosage when administered concomitantly with a strong CYP3A4 inducer [see Dosage and Administration (2.6)].
Antihype	ertensive Drugs	Due to its alpha <sub>1</sub> -adrenergic antagonism, aripiprazole has the potential to enhance the effect of certain antihypertensive agents.	Monitor blood pressure and adjust dose accordingly [see Warnings and Precautions (5.8)].
Benzodia	azepines (e.g., lorazepam)	The intensity of sedation was greater with the combination of oral aripiprazole and lorazepam as compared to that observed with aripiprazole alone. The orthostatic hypotension observed was greater with the combination as compared to that observed with lorazepam alone [see Warnings and Precautions (5.8)].	Monitor sedation and blood pressure. Adjust dose accordingly.

#### 7.2 Drugs Having No Clinically Important Interactions with Aripiprazole

Based on pharmacokinetic studies, no dosage adjustment of aripiprazole is required when administered concomitantly with famotidine, valproate, lithium, and lorazepam. In addition, no dosage adjustment is necessary for substrates of CYP2D6 (e.g., dextromethorphan, fluoxetine, paroxetine, or venlatavine, CYP2C9 (e.g., warfarin, CYP2C19 (e.g., warfarin, escitalopram), or CYP3A4 (e.g., dextromethorphan) when coadministered with aripiprazole. Additionally, no dosage adjustment is

#### 10 OVERDOSAGE

MedDRA terminology has been used to classify the adverse reactions. 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 aripiprazole (42 times the maximum recommended a known bucken active indexed active indextored of 1,200 million and pipezote (42 times the indextinum recommended daily dose) by a patient who fully recovered. Deliberate or accidental overdosage was also reported in children (age 12 years and younger) involving aripiprazole tablet 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 clinically important signs and symptoms observed in one of more patients with an piperactic overlooses (alone or with other substances) include acidosis, aggression, aspartate aminotransferase increased, adrial fibrillation, bradycardia, coma, confusional state, convulsion, blood creatine phosphokinase increased, depressed level of consciousness, hypertension, hypokalemia, hypotension, lethargy, loss of consciousness, QRS complex prolonged, QT prolonged, pneumonia aspiration, respiratory arrest, status epilepticus, and tachycardia.

#### Management of Overdosage

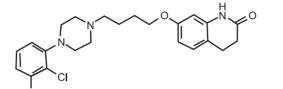
No specific information is available on the treatment of overdose with aripiprazole. An electrocardiogram should be obtained in case of overdosage and if QT interval prolongation is present, cardiac monitoring should be instituted. Otherwise, management of overdose should concentrate on supportive therapy,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

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

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

11 DESCRIPTION

Aripiprazole is a psychotropic drug that is available as aripiprazole tablets. Aripiprazole tablets, USP are chemically designated as 7-[4-[4-(2,3-Dichlorophenyl)-1-piperazinyl] butxy]-3,4-dihydr-2(1H)-quinolinone. The molecular formula is C<sub>23</sub>H<sub>27</sub>Cl<sub>2</sub>N<sub>3</sub>O<sub>2</sub>, and molecular weight is 448.39. The chemical structure is as follows:



Aripiprazole tablets, USP are available in 2 mg, 5 mg, 10 mg, 15 mg, 20 mg, and 30 mg strengths. Inactive ingredients include corn starch, FD&C Blue #2/Indigo Carmine AI, ferric oxide red, ferric oxide yellow, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate and microcrystalline cellulose. FDA approved dissolution test specifications differ from USP

#### 12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of action of aripiprazole in schizophrenia is unclear. However, the efficacy of aripiprazole in the listed indications could be mediated through a combination of partial agonist activity at D<sub>2</sub> and 5-HT<sub>1A</sub> receptors and antagonist activity at 5-HT\_{\rm 2A} receptors.

## 12.2 Pharmacodynamics

Aripiprazole exhibits high affinity for dopamine  $D_2$  and  $D_3$ , serotonin 5-HT<sub>1A</sub> and 5-HT<sub>2A</sub> receptors (K<sub>1</sub> values of 0.34 nM, 0.8 nM, 1.7 nM, and 3.4 nM, respectively), moderate affinity for dopamine  $D_4$ , serotonin 5-HT<sub>2C</sub> and 5-HT<sub>7</sub>, alpha<sub>1</sub>-adrenergic and histamine H<sub>1</sub> receptors (K<sub>1</sub> values of 44 nM, 15 nM, 39 nM, 57 nM, and 61 nM, respectively), and moderate affinity for the serotonin reuptake site (K<sub>i</sub>=98 nM). Aripiprazole has no appreciable affinity for cholinergic muscarinic receptors (IC<sub>50</sub>>1000 nM).

#### 12.3 Pharmacokinetics

Aripiprazole activity is presumably primarily due to the parent drug, aripiprazole, and to a lesser extent, to its major metabolite, dehydro-aripiprazole, which has been shown to have affinities for D<sub>2</sub> receptors similar to the parent drug and represents 40% of the parent drug exposure in plasma. The mean elimination half-lives are about 75 hours and 94 hours for aripiprazole and dehydro-aripiprazole, respectively. Steady-state concentrations are attained within 14 days of dosing for both active moieties. Aripiprazole accumulation is predictable from singledose pharmacokinetics. At steady-state, the pharmacokinetics of aripiprazole is dose-proportional. Elim of an intraction of the second state of the se

Absorption Aripiprazole is well absorbed after administration of the tablet, with peak plasma concentrations occurring within 3 hours to 5 hours; the absolute oral bioavailability of the tablet formulation is 87%. Aripiprazole can be administered with or without food. Administration of a 15 mg aripiprazole tablet with a standard high-fat meal did not significantly affect the  $C_{max}$  or AUC of aripiprazole or its active metabolite, dehydro-aripiprazole, but delayed T<sub>max</sub> by 3 hours for aripiprazole and 12 hours for dehydro-aripiprazole.

#### Distribution

The steady-state volume of distribution of aripiprazole following intravenous administration is high (404 L or 4.9 L/kg), indicating extensive extravascular distribution. At therapeutic concentrations, aripiprazole and its major metabolite are greater than 99% bound to serum proteins, primarily to albumin. In healthy human volunteers administered 0.5 to 30 mg/day aripiprazole for 14 days, there was dose-dependent  $D_2$  receptor occupancy indicating brain penetration of aripiprazole in humans. Metabolism and Elimination

#### Metabolism

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

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

radioactivity was recovered in the urine and feces, respectively. Less than 1% of unchanged aripiprazole was excreted in the urine and approximately 18% of the dose was recovered unchanged in the feces Drug Interaction Studies

Effect of other drugs on the exposures of aripiprazole and dehydro-aripiprazole are summarized in Figure 1 and

#### 14.1 Schizophrenia Adults

The efficacy of aripiprazole in the treatment of schizophrenia was evaluated in five short-term (4-week and 6-week), placebo-controlled trials of acutely relapsed inpatients who predominantly met DSM-III/V criteria for schizophrenia. Four of the five trials were able to distinguish aripiprazole tablets from placebo, but one study, the smallest, did not. Three of these studies also included an active control group consisting of either risperidone le trial) or haloperidol (two trials), but they were not designed to allow for a comparison of aripiprazole and

the active comparators. In the four positive trials for aripiprazole, four primary measures were used for assessing psychiatric signs and symptoms. Efficacy was evaluated using the total score on the Positive and Negative Syndrome Scale (PANSS). The PANSS is a 30-item scale that measures positive symptoms of schizophrenia (7 items), negative symptoms of schizophrenia (7 items), and general psychopathology (16 items), each rated on a scale of 1 (absent) to 7 (extreme); total PANSS scores range from 30 to 210. The Clinical Global Impression (CGI) assessment reflects ssion of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overal the impre clinical state of the patient.

In a 4-week trial (n=414) comparing two fixed doses of aripiprazole (15 or 30 mg/day) to placebo, both doses of aripiprazole were superior to placebo in the PANSS total score (Study 1 in Table 23), PANSS positive subscale, and CGI-severity score. In addition, the 15 mg dose was superior to placebo in the PANSS negative subscale. In a 4-week trial (n=404) comparing two fixed doses of aripiprazole (20 or 30 mg/day) to placebo, both doses of aripiprazole were superior to placebo in the PANSS total score (Study 2 in Table 23), PANSS positive subscale,

PANSS negative subscale, and CGI-severity score. In a 6-week trial (n=420) comparing three fixed doses of aripiprazole (10, 15, or 20 mg/day) to placebo, all three doses of aripiprazole were superior to placebo in the PANSS total score (Study 3 in Table 23), PANSS positive

subscale, and the PANSS negative subscale.

In a 6-week trial (n=367) comparing three fixed doses of aripiprazole (2, 5, or 10 mg/day) to placebo, the 10 mg dose of aripiprazole was superior to placebo in the PANSS total score (Study 4 in Table 23), 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. A biger-term that endoted 510 impatients of outpatients meeting DSM-1V criteria to isolatophrenia who were, by history, symptomatically stable on other antipsychotic medications for periods of 3 months or longer. These patients were discontinued from their antipsychotic medications and randomized to 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  $\geq$ 5 (minimally worse), scores  $\geq$ 5 (moderately severe) on the hostility or uncooperativeness items of the PANSS, or  $\geq$ 20% increase in the PANSS total score. Patients receiving aripiprazole tablets 15 mg/ day experienced a significantly longer time to relapse over the subsequent 26 weeks compared to those receiving placebo (Study 5 in Figure 6)

#### Pediatric Patients

13 to 17

The efficacy of aripiprazole in the treatment of schizophrenia in pediatric patients (13 to 17 years of age) was evaluated in one 6-week, placebo-controlled trial of outpatients who met DSM-IV criteria for schizophrenia and had a PANSS score ≥70 at baseline. In this trial (n=302) comparing two fixed doses of aripiprazole (10 or 30 and a hards access to a provide the second placebo in the PANSS total score (Study 6 in Table 23) 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. Table 23: Schizophrenia Studies

#### Treatment Group Study Primary Efficacy Measure: PANNS LS Mean Placebo-subtracted Mean Change fron Score (SD) Baseline (SE) (95% CI) Aripiprazole Tablets (15 mg/day)<sup>†</sup> Aripiprazole Tablets (30 mg/day)<sup>†</sup> -15.5 (2.40) -11.4 (2.39) -12.6 (-18.9, -6.2) -8.5 (-14.8, -2.1) Study 1 98.5 (17.2) Placebo 100.2 (16.5 -2.9(2.36)-9.6 (-15.4, -3.8) Aripiprazole Tablets (20 mg/day) Study 2 92.6 (19.5) -14.5 (2.23) -9 (-14.8, -3.1) Aripiprazole Tablets (30 mg/day) 94.2 (18.5 -13.9 (2.24) Placebo 94.3 (18.5) -5.0 (2.17) Study 3 Aripiprazole Tablets (10 mg/day) 92.7 (19.5 -15.0 (2.38) -11.7 (2.38) -12.7 (-19, -6.41) 9.4 (-15.71, -3.08) Aripiprazole Tablets (15 mg/day) 93.2 (21.6) Aripiprazole Tablets (20 mg/day) 92.5 (20.9) -14.4 (2.45) 12.1 (-18.53, -5.68) 92.3 (21.8) -2.3 (2.35) Placebo Study 4 Aripiprazole Tablets (2 mg/day) 90.7 (14.5) -8.2 (1.90) -2.9 (-8.29, -2.47 Aripiprazole Tablets (5 mg/day) 92.0 (12.6) -10.6 (1.93) -5.2 (-10.7. -0.19 Aripiprazole Tablets (10 mg/day) -11.3 (1.88) -5.9 (-11.3, -0.58 Placebo 90.8 (13.3) -5.3(1.97)Study 6 Aripiprazole Tablets (10 mg/day) † 93.6 (15.7) -26.7(1.91)-5.5 (-10.7, -0.21)

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval \* Difference (drug minus placebo) in least-squares mean change from baseline

94.0 (16.1)

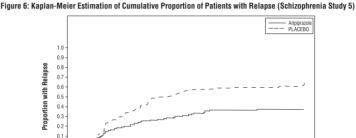
94.6 (15.6)

-21.2(1.93)

<sup>†</sup> Doses statistically significantly superior to placebo.

Aripiprazole Tablets (30 mg/day)

Placebo



Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with aripiprazole tablets and should counsel them in its appropriate use. A patient Medication Guide including information about "Antidepressant Medicines, Depression and other Serious Mental Illnesses, and Suicidal Thoughts or Actions" is available for aripiprazole tablets. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. It should be noted that aripiprazole tablets are not approved as a single agent for treatment of depression and has not been evaluated in diatric major 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 aripiprazole. In some cases, but not all, the urges were reported to have stopped when the dose was reduced or stopped [see Warnings and Precautions (5.7)]. Interference with Cognitive and Motor Performance

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

Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or overthe-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)].

#### 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 withdrawa symptoms (agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder) in a neonate. Advise patients that there is a pregnancy registry that monitors pregnancy outcomes in women exposed to Aripiprazole during pregnancy [see Use in Specific Populations (8.1)].

#### Lactation

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

# CAMBER

Manufactured for:

# Camber Pharmaceuticals, Inc. Piscataway, NJ 08854.

changed.

or feelings.

thoughts about suicide or dying

feeling very agitated or restless

acting aggressive, being angry, or violent acting on dangerous impulses an extreme increase in activity and talking (mania)

What else do I need to know about antidepressant medicines?

antidepressant medicine suddenly can cause other symptoms

other unusual changes in behavior or mood

of the medicine prescribed for you or your fan

attempts to commit suicide

new or worse depression

new or worse anxiety

trouble sleeping (ins

new or worse irritability

panic attacks

-7.4 (-12.7, -2.13)

By: HETEROTM etero Labs Limited, Unit V, Polepally, Jadcherla, Mahabubnagar - 509 301, India.

#### Revised: 05/2025

MEDICATION GUIDE Aripiprazole Tablets USP (ar'' i pip' ra zole)

What is the most important information I should know about aripiprazole tablets For other side effects, also see "What are the possible side effects of aripiprazole tablets?")

- erious side effects may happen when you take aripiprazole tablets, including:
- Increased risk of death in elderly patients with dementia-related psychosis: Medicines like aripiprazol tablets can raise the risk of death in elderly people who have lost touch with reality (psychosis) due to confusion and memory loss (dementia). Aripiprazole tablets are not approved for the treatment of patients
- with dementia-related psychosis. Risk of suicidal thoughts or actions: Antidepressant medicines, depression and other serious menta
- ses, and suicidal thoughts or actions: Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, and young adults within the first few months of treatment. Depression and other serious mental illnesses are the most important causes of suicidal thoughts and

actions. Some people may have a particularly high risk of having suicidal thoughts or actions. These include people who have (or have a family history of) suicidal thoughts or actions. How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?

Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts,

Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts

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

between visits as needed, especially if you have concerns about symptoms

Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare provide

feelings. This is very important when an antidepressant medicine is started or when the dose is

cecessary for valproate, lithium, lamotrigine, lorazepam, or sertraline when coadministered with aripiprazole [see Clinical Pharmacology (12.3)].

## 8 USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy

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-programs/pregnancyregistry/

#### **Risk Summary**

Hisk Summary 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 data from published epidemiologic studies of pregnant women exposed to aripiprazole have not established a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes (see *Data*). There are risks to the mother associated with untreated schizophrenia, and with exposure to antipsychotics, including aripiprazole, during pregnancy (see *Clinical Considerations*). Aripiprazole exposure during pregnancy can have variable effects on milk supply in the post-partum period (*see Use in Specific Populations* (8.2)).

In animal reproduction studies, aripiprazole administration during organogenesis in rats and/or rabbits at doses 10 and 19 times, respectively, the maximum recommended human dose (MRHD) of 30 mg/day based on mg/ m<sup>2</sup> body surface area, produced fetal death, decreased fetal weight, undescended testicles, delayed skeletal positication, skeletal abnormalities, and diaphragmatic hernia. Arripirazole administration during the pre- and post-natal period in rats at doses 10 times the MRHD based on mg/m<sup>2</sup> 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 and a background rate of 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 including increased risk of relapse, hospitalization, and suicide. Schizophrenia is 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. 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. D<u>ata</u>

#### Human Data

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 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/m<sup>2</sup> body surface area, a slight prolongation of gestation and delay in fetal development, as evidenced by decreased fetal weight and undescended testes, were observed at 10 times the MRHD. Delayed skeletal ossification was observed at 3 and 10 times the MRHD. Delayed skeletal ossification was observed at 3 and 10 times the MRHD. Delivered offspring had increased incidences of hepatodiaphragmatic nodules and diaphragmatic hernia 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.

In pregnant rats injected intravenously with aripiprazole during organogenesis at doses of 3, 9, and 27 mg/kg/day, which are 1, 3, and 9 times the MRHD of 30 mg/day based on mg/m<sup>2</sup> body surface area, decreased fetal weight and delayed skeletal ossification were observed at 9 times the MRHD; this dose also caused maternal toxicity. In pregnant rabbits treated orally with aripiprazole during organogenesis at doses of 10, 30, and 100 mg/kg/day which are 6, 19, and 65 times the MRHD of 30 mg/day based on mg/m<sup>2</sup> body surface area, decreased maternal

food consumption, and increased abortions as well as increased fetal mortality were observed at 55 times the MRHD. Decreased fetal weight and increased incidence of fused sternebrae were observed at 19 and 65 times the MRHD.

In pregnant rabbits injected intravenously with aripiprazole during organogenesis at doses of 3, 10, and 30 mg/ kg/day, which are 2, 6, and 19 times the MRHD of 30 mg/day based on mg/m<sup>2</sup> body surface area, decreased fetal weight, increased fetal abnormalities (primarily skeletal), and decreased fetal skeletal ossification were observed at 19 times the MRHD; this dose also caused maternal toxicity. The fetal no-effect dose was 10 mg/kg/day, which is 6 times the MRHD.

In rats treated orally with aripiprazole peri- and postnatally from gestation Day 17 through postpartum Day 21 at doses of 3, 10, and 30 mg/kg/day which are 1, 3, and 10 times the MRHD of 30 mg/day based on mg/m<sup>2</sup> 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/m<sup>2</sup> body surface area, increased stillbirths were observed at 3 and 6 times the MRHD; and decreases in early postnatal pup weight and survival were observed at 6 times the MRHD; these doses also caused some maternal toxicity. There were no effects on postnatal behavioral and reproductive development.

#### 8.2 Lactation

#### **Risk Summary**

Aripiprazole is present in human breast milk. Based on published case reports and pharmacovigilance reports, aripiprazole exposure during pregnancy and/or the postpartum period can lead to variable effects on milk supply in the post-partum period, including clinically relevant decreases in milk supply which may be reversible with discontinuation of the drug. There are also reports of aripiprazole exposure during pregnancy and no maternal milk supply in the post-partum period. Effects on milk supply are likely mediated through decreases in prolactin levels, which have been observed [see Adverse Reactions (6.1)]. Monitor the breastfed infant for dehydration and lack of appropriate weight gain. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for aripiprazole and any potential adverse effects on the breastfed infant from aripiprazole or from the underlying maternal condition.

## 8.4 Pediatric Use

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

The pharmacokinetics of aripipracile and dehydro-aripipracile 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)]. Schizophrenia

Safety and effectiveness in pediatric patients with schizophrenia were established in a 6-week, placebo-controlled clinical trial in 202 pediatric patients aged 13 to 17 years [see Dosage and Administration (2.1), Adverse Reactions (6.1), and Clinical Studies (14.1)]. Although maintenance efficacy in pediatric patients has not been systematically (0.7), and climical soluties (14.7). Antiologin manuemance encacy in pediatic patients has not been systematican evaluated, maintenance efficacy can be extrapolated from adult data along with comparisons of aripiprazol pharmacokinetic parameters in adult and pediatric patients.

#### Irritability Associated with Autistic Disorder

Irritability Associated with Autistic Disorder Safety and effectiveness in pediatric patients demonstrating irritability associated with autistic disorder were established in two 8-week, placebo-controlled clinical trials in 212 pediatric patients aged 6 to 17 years [see Indications and Usage (1), Dosage and Administration (2.4), Adverse Reactions (6.1), and Clinical Studies (14.4)]. A maintenance trial was conducted in pediatric patients (6 to 17 years of age) with irritability associated with autistic disorder. The first phase of this trial was an open-label, flexibly dosed (arripiprazole 2 to 15 mg/day) phase in which patients were stabilized (defined as >25% improvement on the ABC-I subscale, and a CGI-I rating of "much improved" or "very much improved") on aripiprazole for 12 consecutive weeks. Overall, 85 patients were stabilized and entered the second, 16-week, double-blind phase where they were randomized to either continue aripiprazole treatment to switch to nearboard. aripiprazole treatment or switch to placebo. In this trial, the efficacy of aripiprazole for the maintenance treatment of irritability associated with autistic disorder was not established.

#### Tourette's Disorder

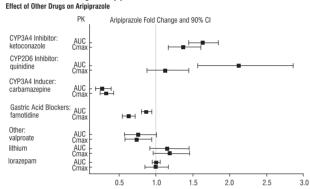
Safety and effectiveness of aripiprazole in pediatric patients with Tourette's Disorder were established in one Sarety and encurveness of an physical encurve and patients with routeuts subsorted were established in one 8-week (aged 7 to 17 years) and one 10-week trial (aged 6 to 18 years) in 194 pediatric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

#### Juvenile Animal Studies

ed mortality. CNS clinical signs, impaired memory and learning, and delayed Aripiprazole in juvenile rats ca

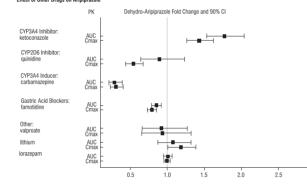
is expected when extensive metabolizers of CYP2D6 are administered with both strong CYP2D6 and CYP3A4 inhibitors. A 3-fold increase in mean C<sub>max</sub> and AUC values at steady-state is expected in poor metabolizers of CYP2D6 administered with strong CYP3A4 inhibitors.

## Figure 1: The Effect of Other Drugs on Aripiprazole Pharmacokinetics



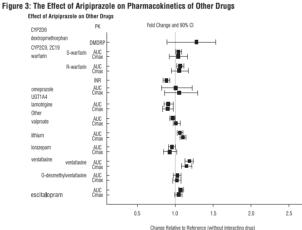
Change Relative to Reference (without interacting drug) Figure 2: The Effect of Other Drugs on Dehydro-Aripiprazole Pharmacokinetics

#### Effect of Other Drugs on Aripiprazole



Change Relative to Reference (without interacting drug)

The effect of aripiprazole on the exposures of other drugs are summarized in Figure 3.



Exposure of aripiprazole and dehydro-aripiprazole in specific populations are summarized in Figure 4 and Figure respectively. In addition, in pediatric patients (10 to 17 years of age) administered with aripiprazole (20 mg to 30 mg), the body weight corrected aripiprazole clearance was similar to the adults. Figure 4: Effect of Intrinsic Factors on Aripiprazole Pharmacokinetics

Specific Populations

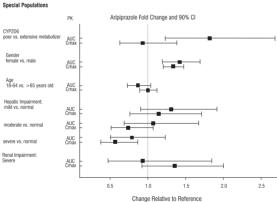
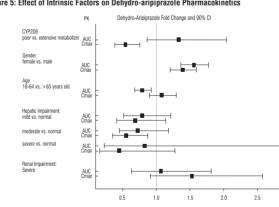


Figure 5: Effect of Intrinsic Factors on Dehydro-aripiprazole Pharmacokinetics



Change Relative to Reference

0.0 -		المر												
					Numb	er of Su	bjects at	Risk						
Aripiprazole	148	138	111	104	96	92	88	84	78	76	75	73	71	22
PLACEBO	149	139	105	89	76	66	59	53	50	49	46	46	45	12
	0	14	28	42	56	70	84	98	112	126	140	154	168	182
	U	14	28	42						120	140	154	100	182
					Day	s fron	n Rand	lomiza	ition					

# 14.4 Irritability Associated with Autistic Disorder

Pediatric Patients The efficacy of aripiprazole in the treatment of irritability associated with autistic disorder was established in two 8-week, placebo-controlled trials in pediatric patients (6 to 17 years of age) who met the DSM-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 patients were under 13 years of age.

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

irritability in autistic disorder. The results of these trials are as follows:

In one of the 8-week, placebo-controlled trials, children and adolescents with autistic disorder (n=98), aged 6 to 17 years, received daily doses of placebo or aripiprazole 2 to 15 mg/day. aripiprazole, starting at 2 mg/day with increases allowed up to 15 mg/day based on clinical response, significantly improved scores on the ABC-I subscale and on the CGI-I scale compared with placebo. The mean daily dose of aripiprazole at the end of 8-week treatment was 8.6 mg/day (Study 1 in Table 26).

In the other 8-week, placebo-controlled trial in children and adolescents with autistic disorder (n=218), aged 6 In the other 6-week, placebo-controlled that in trinden and addressents with additional to the  $(n=2,r_0)$ , aged to 17 years, three fixed does 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 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 26). All three doses of aripiprazole significantly improved scores on the ABC-I subscale compared with placebo.

#### Table 26: Irritability Associated with Autistic Disorder Studies (Pediatric)

		Primary Efficacy Measure: ABC-I				
Study Number	Treatment Group	Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracte Difference* (95% Cl)		
Study 1	Aripiprazole (2 to 15 mg/day) <sup>†</sup>	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) <sup>†</sup>	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)			

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

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

<sup>†</sup> Doses statistically significantly superior to placebo

## 14.5 Tourette's Disorder

## Pediatric Patients

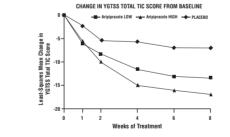
The efficacy of aripiprazole in the treatment of Tourette's Disorder was established in one 8- week (7 to 17 years of The chicady of allophable in dealine tradition burgets of both the standard model of th Tic Severity Scale (YGTSS). The YGTSS is a fully validated scale designed to measure current tic 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 (CGL-TS), a clinician-determined summary measure that takes into account all available patient information. Over 65% of these patients were under 13 years of age. The primary outcome measure in both trials was the change from baseline to endpoint in the TTS of the YGTSS.

Ratings for the TTS are made along 5 different dimensions on a scale of 0 to 5 for motor and vocal tics each. Summation of these 10 scores provides a TTS (i.e., 0 to 50).

#### The results of these trials are as follows:

In the 8-week, placebo-controlled, fixed-dose trial, children and adolescents with Tourette's Disorder (n=133). In the 8-week, placebo-controlled, ixed-dose trail, children and adolescents with 100 traffets Disorder (n=133), aged 7 to 17 years, were randomized 11:11 to low dose aripiprazole, high dose aripiprazole, cor 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/day with a target dose of 5 mg/day after 2 days. Patients  $\geq$ 50 kg in the low dose aripiprazole group, started at 2 mg/day increased to 5 mg/day after 2 days. With a subsequent increase to a target dose of 10 mg/day at Day 7. Patients <50 kg in the high dose aripiprazole group started at 2 mg/day increased to 40 kg in the high dose aripiprazole group started at 2 mg/day increased to 40 kg in the high dose aripiprazole group started at 2 mg/day increased to 40 kg in the high dose aripiprazole group started at 2 mg/day increased to 40 kg in the high dose aripiprazole group started at 2 mg/day increased to 40 kg in the high dose aripiprazole group started at 2 mg/day increased to 40 kg in the high dose aripiprazole group started at 2 mg/day increased to 40 kg in the high dose aripiprazole group started at 2 mg/day increased to 40 kg in the high dose aripiprazole group started at 2 mg/day increased to 40 kg in the high dose aripiprazole group started at 2 mg/day increased to 40 kg in the high dose aripiprazole group started at 40 kg interest to 40 kg in the high dose aripiprazole group started at 40 kg interest to 40 kg buse on to fing day all by 7. Patients <50 kg in the high tuse antipitable globp state of a high day increased to 5 mg/day after 2 days, with a subsequent increase to a target dose of 10 mg/day at Day 7. Patients <50 kg in the high dose aripiprazole group, started at 2 mg/day increased to 5 mg/day after 2 days, with a subsequent increase to a dose of 10 mg/day at Day 7. Patients <50 kg in the high dose aripiprazole group, started at 2 mg/day increased to 5 mg/day after 2 days, with a subsequent increase to a dose of 10 mg/day at Day 7. Patients <50 kg in the high dose groups) demonstrated statistically significantly improved scores on the YGTSS TTS (Study 1 in Table 27) 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 actives of the VGTSS TTS scale compared with placebo (Study 2 in Table 27). The mean daily dose of aripiprazole at the end of 10-week treatment was 6.54 mg/day.

#### Table 27: 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 Tablets (low dose) <sup>†</sup> Aripiprazole Tablets (high dose) <sup>†</sup> Placebo	29.2 (5.63) 31.2 (6.40) 30.7 (5.95)	-13.4 (1.59) -16.9 (1.61) -7.1 (1.55)	-6.3 (-10.2, -2.3) -9.9 (-13.8, -5.9) 		
Study 2	Aripiprazole Tablets (2 to 20 mg/day) <sup>†</sup> Placebo	28.3 (5.51) 29.5 (5.60)	-15.0 (1.51) -9.6 (1.64)	-5.3 (-9.8, -0.9) 		

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval. \*Difference (drug minus placebo) in least-squares mean change from baseline.

#### <sup>†</sup>Doses statistically significantly superior to placebo. 16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied Aripipraciole tablets, USP 2 mg are light green to green, modified rectangular, bevel edged biconvex plain to mottled tablets debossed with 'I' on one side and '94' on other side.

Bottles of 30 Tablets NDC 31722-819-30

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

Never stop an antidepressant medicine without first talking to a healthcare provider. Stopping an

Antidepressants are medicines used to treat depression and other illnesses. It is important to discuss

all the risks of treating depression and also the risks of not treating it. Patients and their families o other caregivers should discuss all treatment choices with the healthcare provider, not just the use o

Antidepressant medicines have other side effects. Talk to the healthcare provider about the side effect

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

#### What are aripiprazole tablets?

antidepressants.

- Aripiprazole tablets are prescription medicine used to treat: Schizophrenia
- irritability associated with autistic disorder
- Tourette's Disorder
- t is not known if aripiprazole tablets are safe or effective in children: under 13 years of age with schizophrenia
- under 6 years of age with irritability associated with autistic disorder
- under 6 years of age with Tourette's Disorder
- Do not take aripiprazole tablets if you are allergic to aripiprazole or any of the ingredients in aripiprazole tablets. See the end of this Medication Guide for a complete list of ingredients in aripiprazole tablets.

# Before taking aripiprazole tablets, tell your healthcare provider about all your medical conditions, including

- diabetes or high blood sugar in you or your family: your healthcare provider should check your blood suga before you start aripiprazole tablets and also during therapy.
- seizures (convulsions).
- low or high blood pressure. heart problems or stroke.

tablets works.

when you get a new medicine.

How should I take aripiprazole tablets?

right away, or go to the nearest hospital emergency room.

In hot weather, stay inside in a cool place if possible. Stay out of the sun. Do not wear too much or heavy clothing.

What should I avoid while taking aripiprazole tablets?

What are the possible side effects of aripiprazole tablets?

Problems with your metabolism such as:

need to urinate more than usual feel very hungry

feel sick to your stomach feel confused, or your breath smells fruity

rising too quickly from a sitting or lying position.

that can cause fractures or other injuries.

avoid while taking aripiprazole tablets?

Low white blood cell count

Seizures (convulsions)

nausea

vomiting

constipation

blurred vision

feeling sleepy

vomiting

fatigue

headache

upper respiratory illness

headache

• Increased fat levels (cholesterol and triglycerides) in your blood.

Weight gain. You and your healthcare provider should check your weight regularly

during your treatment

aripiprazole tablets

feel verv thirsty

feel weak or tired

Aripiprazole tablets may cause serious side effects, including:

Avoid getting over-heated or dehydrated.

Do not over-exercise.

Drink plenty of water.

- pregnancy or plans to become pregnant. It is not known if aripiprazole tablets will harm your unborn baby. If you become pregnant while receiving aripiprazole tablets, talk to your healthcare provider about registering with the National Pregnancy Registry for Atypical Antipsychotics. You can register by calling 1-866-961-2388 or go to http://womensmentalhealth.org/clinical-and-research-programs
- pregnancyregistry/ breast-feeding or plans to breast-feed. Aripiprazole passes into your breast milk. Talk to your healthcar provider about the best way to feed your baby if you receive aripiprazole tablets

#### low white blood cell count Tell your healthcare provider about all the medicines that you take, including prescription and over-the

counter medicines, vitamins, and herbal supplements. Aripiprazole tablets and other medicines may affect each other causing possible serious side effects. Aripiprazole tablets may affect the way other medicines work, and other medicines may affect how aripiprazole

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

Take aripiprazole tablets exactly as your healthcare provider tells you to take it. Do not change the dose or stop taking aripiprazole tablets yourself. Aripiprazole tablets can be taken with or without food. Aripiprazole tablets should be swallowed whole. If you miss a dose of aripiprazole tablets, take the missed dose as soon as you remember. If it is almost

time for the next dose, just skip the missed dose and take your next dose at the regular time. Do not take two doses of aripiprazole tablets at the same time. If you take too much aripiprazole, call your healthcare provider or poison control center at 1-800-222-1222

Do not drive, operate heavy machinery, or do other dangerous activities until you know how aripiprazole tablets affects you. Aripiprazole tablets may make you drowsy.

Neuroleptic malignant syndrome (NMS). Tell your healthcare provider right away if you have some or all of the following symptoms: high fever, stiff muscles, confusion, sweating, changes in pulse, heart rate, and

blood pressure. These may be symptoms of a rare and serious condition that can lead to death. Call your

Uncontrolled body movements (tardive dyskinesia). Aripiprazole tablets may cause movements that yo

cannot control in your face, tongue, or other body parts. Tardive dyskinesia may not go away, even if you stop receiving aripiprazole tablets. Tardive dyskinesia may also start after you stop receiving aripiprazole

High blood sugar (hyperglycemia) and diabetes. Increases in blood sugar can happen in some

people who take aripiprazole tablets. Extremely high blood sugar can lead to coma or death. If you have diabetes or risk factors for diabetes (such as being overweight or a family history of diabetes), your healthcare provider should check your blood sugar before you start aripiprazole tablets and

Call your healthcare provider if you have any of these symptoms of high blood sugar while receiving

Unusual urges. Some people taking aripiprazole tablets have had unusual urges, such as gambling, binge eating or eating that you cannot control (compulsive), compulsive shopping and sexual urges.

Orthostatic hypotension (decreased blood pressure). Lightheadedness or fainting may happen whe

Falls. Aripiprazole tablets may make you sleepy or dizzy, may cause a decrease in your blood

Problems with control of your body temperature especially when you exercise a lot or are in an
area that is very hot. It is important for you to drink water to avoid dehydration. See "What should

· Difficulty swallowing that can cause food or liquid to get into your lungs

The most common side effects of aripiprazole tablets in adults include:

pressure when changing position and can slow your thinking and motor skills which may lead to falls

dizziness

insomnia

restlessness

insomnia

nausea

stuffy nose

weight gain

increased saliva or drooling

inner sense of restlessness/need to move

anxiety

f you or your family members notice that you are having unusual urges or behaviors, talk to your healthcare

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

Stroke in elderly people (cerebrovascular problems) that can lead to death

healthcare provider right away if you have any of these symptoms.

sexual maturation when administered at oral doses of 10, 20, 40 mg/kg/day from weaning (21 days old) through aturity (80 days old). At 40 mg/kg/day, mortality, decreased activity, splayed hind limbs, hunched posture, ataxia, tremors and other CNS signs were observed in both genders. In addition, delayed sexual maturation was observed in males. At all doses and in a dose-dependent manner, impaired memory and learning, increased motor activity, and histopathology changes in the pituliary (atrophy), adrenals (adrenals (adrenocortical hypertrophy), mammary glands (hyperplasia and increased secretion), and female reproductive organs (vaginal mucification, endometrial atrophy, decrease in ovarian corpora lutea) were observed. The changes in female reproductive organs were considered secondary to the increase in prolactin serum levels. A No Observed Adverse Effect Level (NOAEL) could not be determined and, at the lowest tested dose of 10 mg/kg/day, there is no safety margin relative to the systemic exposures (AUC<sub>0 to 24</sub>) for aripiprazole or its major active metabolite in adolescents at the maximum recommended pediatric dose of 15 mg/day. All drug-related effects were reversible after a 2-month recovery period, and most of the drug effects in juvenile rats were also observed in adult rats from previously conducted studies

Aripiprazole in juvenile doos (2 months old) caused CNS clinical signs of tremors, hypoactivity, ataxia, recumbency and limited use of hind limits when administered orally for 6 months at 3,10,30 mg/kg/day. Mean body weight and weight gain were decreased up to 18% in females in all drug groups relative to control values. A NOAEL could not be determined and, at the lowest tested dose of 3 mg/kg/day, there is no safety margin relative to the systemic The determined and, at the lowest estep upon of a fight  $M_{0}$  and  $M_{0}$  a

#### 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  $\geq$ 65 years old and 799 (6%) were ≥75 years old. Placebo-controlled studies of aripiprazole in schizophrenia or other indications did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients.

Aripiprazole is not approved for the treatment of patients with psychosis associated with Alzheimer's disease [see Boxed Warning and Warnings and Precautions (5.1)].

#### 8.6 CYP2D6 Poor Metabolizers

Dosage adjustment is recommended in known CYP2D6 poor metabolizers due to high aripiprazole concentrations. Approximately 8% of Caucasians and 3 to 8% of Black/African Americans cannot metabolize CYP2D6 substrates and are classified as poor metabolizers (PM) [see Dosage and Administration (2.6) and Clinical Pharmacology

#### 8.7 Henatic and Benal Imnairment

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.

#### 9.2 Abuse

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

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

#### 13 NONCLINICAL TOXICOLOGY 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility Carcinogenesis

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 mo/m<sup>2</sup> body surface area, respectively). In addition, SD rats were dosed orally for 2 years at 10, 20, 40, and 60 mg/kg/day, which are 3, 6, 13 and 19 times the MRHD based on mg/m<sup>2</sup> body surface area. Aripiprazole did not induce tumors in male mice or male rats. In female mice, the incidences of pituitary gland adenomas and mammary gland adenocarcinomas and adenoacanthomas were increased at dietary doses of 3 to 30 mg/kg/day (0.5 to 5 times the MRHD). In female rats, the incidence of mammary gland fibroadenomas was increased at a dietary dose of 10 mg/kg/day (3 times the MRHD); and the incidences of adrenocortical carcinomas and combined enocortical adenomas/carcinomas were increased at an oral dose of 60 mg/kg/day (19 times the MRHD).

An increase in mammary, pituitary, and endocrine pancreas neoplasms has been found in rodents after chronic administration of other antipsychotic drugs and is considered to be mediated by prolonged dopamine  $D_2$ -receptor antagonism and hyperprolactinemia. Serum prolactin was not measured in the aripiprazole carcinogenicity studies. However, increases in serum prolactin levels were observed in female mice in a 13-week dietary study at the doses associated with mammary gland and pituitary tumors. Serum prolactin was not increased in female rats in 4 week and 13-week dietary studies at the dose associated with mammary gland tumors. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unclear.

#### **Mutagenesis**

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

#### 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 MBHD of 30 mg/day based on mg/m<sup>2</sup> body surface area. Estrus cycle irregularities and increased corpora lutea were seen at all doses, but no imp was seen. Increased pre-implantation loss was seen at 2 and 6 times the MRHD, and decreased fetal weight was seen at 6 times the MRHD.

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

#### 13.2 Animal Toxicology and/or Pharmacology

Aripiprazole produced retinal degeneration in albino rats in a 26-week chronic toxicity study at a dose of 60 mg/kg/ An phrace producer terms degeneration in a non-rate many rate are very enrolled toxicity study at a use or to mg/ng/ day and in a 2-year carcinogenicity study at doses of 40 and 60 mg/kg/day which are 13 and 19 times the MRHD of 30 mg/day based on mg/m<sup>2</sup> body surface area. Evaluation of the retinas of albino mice and of monkeys did not reveal evidence of retinal degeneration. Additional studies to further evaluate the mechanism have not been erformed. The relevance of this finding to human risk is unknown.

#### 14 CLINICAL STUDIES

Efficacy of aripiprazole was established in the following adequate and well-controlled trials:

- Four short-term trials and one maintenance trial in adult patients and one short-term trial in adolescents (ages 13 to 17 years) with schizophrenia [see Clinical Studies (14.1)] Two short-term trials in pediatric patients (ages 6 to 17 years) for the treatment of irritability associated with
- autistic disorder [see Clinical Studies (14.4)]
- Two short-term trials in pediatric patients (ages 6 to 18 years) with Tourette's Disorder [see Clinical Studies (14.5)]

	NEO OTTEL OTO OT
Bottles of 500 Tablets	NDC 31722-819-05
Blister card of 10 Unit dose tablets	NDC 31722-819-31
Rister pack of 250 (25 x 10) Unit does tablete	NDC 31792-810-32

Aripiprazole tablets, USP 5 mg are light blue to blue, modified rectangular, bevel edged biconvex tablets debossed with 'I' on one side and '95' on other side.

Rottles of 100 Tablets

Bottles of 30 Tablets	NDC 31722-820-3
Bottles of 100 Tablets	NDC 31722-820-0
Bottles of 500 Tablets	NDC 31722-820-0
Blister card of 10 Unit dose tablets	NDC 31722-820-3
Blister pack of 250 (25 x 10) Unit dose tablets	NDC 31722-820-3

Aripiprazole tablets, USP 10 mg are light pink to pink, modified rectangular, bevel edged biconvex plain to mottled tablets debossed with 'I' on one side and '96' on other side.

Bottles of 30 Tablets	NDC 31722-827-30
Bottles of 100 Tablets	NDC 31722-827-01
Bottles of 500 Tablets	NDC 31722-827-05
Blister card of 10 Unit dose tablets	NDC 31722-827-31
Blister nack of 250 (25 x 10) Unit dose tablets	NDC 31722-827-32

Aripiprazole tablets, USP 15 mg are light yellow to yellow, round, bevel edged biconvex plain to mottled tablets ossed with 'I' on one side and '97' on other side

Bottles of 30 Tablets	NDC 31722-828-30
Bottles of 100 Tablets	NDC 31722-828-01
Bottles of 500 Tablets	NDC 31722-828-05
Blister card of 10 Unit dose tablets	NDC 31722-828-31
Blister pack of 250 (25 x 10) Unit dose tablets	NDC 31722-828-32

Aripiprazole tablets. 20 mg are white to off-white, round, bevel edged biconvex tablets debossed with 'I' on one side and '98' on other side

Bottles of 30 Tablets	NDC 31722-829-30
Bottles of 100 Tablets	NDC 31722-829-01
Bottles of 500 Tablets	NDC 31722-829-05
Blister card of 10 Unit dose tablets	NDC 31722-829-31
Blister pack of 250 (25 x 10) Unit dose tablets	NDC 31722-829-32

Aripiprazole tablets, USP 30 mg are light pink to pink, round, bevel edged biconvex plain to mottled tablets debossed with 'I' on one side and '99' on other side.

Bottles of 30 Tablets	NDC 31722-830-30
Bottles of 100 Tablets	NDC 31722-830-01
Bottles of 500 Tablets	NDC 31722-830-05
Blister card of 10 Unit dose tablets	NDC 31722-830-31
Blister pack of 250 (25 x 10) Unit dose tablets	NDC 31722-830-32

#### Storage

Store at 20° to 25° C (68° to 77°F) [see USP Controlled Room Temperature].

#### 17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

#### Clinical Worsening of Depression and Suicide Risk

Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, radiation, prior and the tene tenegrees should be the tenegrees to be derived to be the tenegrees tenegrees and the tenegrees and tene ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to look for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior **and indicate a need for very close monitoring and possibly changes in the medication** [see Warnings and Precautions (5.3)].

uncontrolled movement such as restless tremor

The most common side effects of aripiprazole tablets in children include:

#### hese are not all the possible side effects of aripiprazole tablets.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088

#### How should I store aripiprazole tablets? Store aripiprazole tablets at 68° to 77°F (20° to 25° C).

increased or decreased appetite

Keep aripiprazole tablets and all medicines out of the reach of children.

#### General information about the safe and effective use of aripiprazole tablets

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

#### What are the ingredients in arigiprazole tablets?

Active ingredient: aripiprazole USP Inactive ingredients: corn starch, FD&C Blue #2/Indigo Carmine AI, ferric oxide red, ferric oxide yellow hydroxypropyl cellulose, lactose monohydrate, magnesium stearate and microcrystalline cellulose

Medication Guide available at http://camberpharma.com/medication-guides



Manufactured for: Camber Pharmaceuticals, Inc. Piscataway, NJ 08854.

#### BV: HETEROTM etero Labs Limited, Unit V, Polepally, Jadcherla, Mahabubnagar - 509 301, India

For more information, call 1-866-495-1995

This Medication Guide has been approved by the U.S. Food and Drug Administration Revised: 05/2025

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