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

ARISTADA® (aripiprazole lauroxil) extended-release injectable suspension, for intramuscular use
Initial U.S. Approval: 2015

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS
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. (5.1)**
- **ARISTADA is not approved for the treatment of patients with dementia-related psychosis. (5.1)**

RECENT MAJOR CHANGES

Warnings and Precautions, Falls (5.8) 02/2017
Warnings and Precautions, Pathological Gambling and Other Compulsive Behaviors (5.6) 07/2016

INDICATIONS AND USAGE

ARISTADA is an atypical antipsychotic indicated for the treatment of schizophrenia (1).

DOSAGE AND ADMINISTRATION

- To be administered by intramuscular injection in the deltoid (441 mg dose only) or gluteal (441 mg, 662 mg or 882 mg) muscle by a healthcare professional (2.1).
- For patients naïve to aripiprazole, establish tolerability with oral aripiprazole prior to initiating treatment with ARISTADA (2.1).
- ARISTADA can be initiated at a dose of 441 mg, 662 mg or 882 mg administered monthly or 882 mg dose every 6 weeks (2.1).
- In conjunction with the first ARISTADA injection, administer treatment with oral aripiprazole for 21 consecutive days (2.1).
- Dosing regimen adjustments may be required for missed doses (2.2).
- Dose adjustments are required for 1) known CYP2D6 poor metabolizers and 2) for patients taking CYP3A4 inhibitors, CYP2D6 inhibitors, or CYP3A4 inducers for more than 2 weeks (2.4).

DOSAGE FORMS AND STRENGTHS

For extended-release injectable suspension: 441 mg, 662 mg or 882 mg single-use pre-filled syringe (3)

CONTRAINDICATIONS

Known hypersensitivity to aripiprazole (4)

WARNINGS AND PRECAUTIONS

- *Cerebrovascular Adverse Reactions in Elderly Patients with Dementia-Related Psychosis:* Increased incidence of cerebrovascular adverse reactions (e.g., stroke, transient ischemia attack, including fatalities) (5.2).
- *Neuroleptic Malignant Syndrome*: Manage with immediate discontinuation and close monitoring (5.3).
- *Tardive Dyskinesia*: Discontinue if clinically appropriate (5.4).
- *Metabolic Changes*: Monitor for hyperglycemia, dyslipidemia, and weight gain (5.5).
- *Pathological Gambling and Other Compulsive Behaviors:* Consider dose reduction or discontinuation (5.6)
- *Orthostatic Hypotension*: Monitor heart rate and blood pressure and warn patients with known cardiovascular or cerebrovascular disease, and risk of dehydration or syncope (5.7).
- *Leukopenia, Neutropenia, and Agranulocytosis*: Perform complete blood counts in patients with a history of a clinically significant low white blood cell (WBC) count. Consider discontinuation if clinically significant decline in WBC in the absence of other causative factors (5.9 5.8).
- *Seizures*: Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold (5.10).
- *Potential for Cognitive and Motor Impairment*: Use caution when operating machinery (5.11).

ADVERSE REACTIONS

Most commonly observed adverse reaction with ARISTADA (incidence ≥5% and at least twice that for placebo) was akathisia (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Alkermes, Inc. at 1-866-274-7823 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

USE IN SPECIFIC POPULATIONS

- *Pregnancy:* May cause extrapyramidal and/or withdrawal symptoms in neonates in women exposed during the third trimester of pregnancy (8.1).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 02/2017

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FULL PRESCRIBING INFORMATION

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

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. ARISTADA is not approved for the treatment of patients with dementia-related psychosis [*see Warnings and Precautions* (5.1)].

1. INDICATIONS AND USAGE

ARISTADA is indicated for treatment of schizophrenia *[see Clinical Studies (14)]*.

2. DOSAGE AND ADMINISTRATION

2.1. Treatment of Schizophrenia

ARISTADA is only to be administered as an intramuscular injection by a healthcare professional. For patients who have never taken aripiprazole, establish tolerability with oral aripiprazole prior to initiating treatment with ARISTADA. Due to the half-life of oral aripiprazole, it may take up to 2 weeks to fully assess tolerability. Refer to the prescribing information of oral aripiprazole for the recommended dosage and administration of the oral formulation.

Depending on individual patient's needs, treatment with ARISTADA can be initiated at a dose of 441 mg, 662 mg or 882 mg administered monthly, which corresponds to 300 mg, 450 mg and 600 mg of aripiprazole, respectively. Treatment may also be initiated with the 882 mg dose every 6 weeks *[see Clinical Pharmacology (12.3)]*.

Administer ARISTADA either in the deltoid muscle (441 mg dose only) or gluteal muscle (441 mg, 662 mg or 882 mg).

Table 1: ARISTADA Dosing Frequency and Site of Injection

Dose	Dosing Frequency	Site of Intramuscular Injection
441 mg	Monthly	Deltoid or Gluteal
662 mg	Monthly	Gluteal
882 mg	Monthly or every 6 weeks	Gluteal

Use the following ARISTADA doses for patients who are stabilized on oral aripiprazole, as shown in Table 2.

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Table 2: ARISTADA Doses Based on Oral Aripiprazole Total Daily Dose

Oral Aripiprazole Dose	Intramuscular ARISTADA Dose
10 mg per day	441 mg per month
15 mg per day	662 mg per month
20 mg or higher per day	882 mg per month

In conjunction with the first ARISTADA injection, administer treatment with oral aripiprazole for 21 consecutive days.

Dose may be adjusted as needed. When making dose and dosing interval adjustments, the pharmacokinetics and prolonged-release characteristics of ARISTADA should be considered *[see Clinical Pharmacology (12.3)]*.

2.2. Missed Doses

When a dose is missed, administer the next injection of ARISTADA as soon as possible. If the time elapsed since the last ARISTADA injection exceeds the length of time noted in Table 3, use oral aripiprazole supplementation with the next ARISTADA injection as recommended below.

Table 3: Recommendation for Concomitant Oral Aripiprazole Supplementation Following Missed Doses[a]

Dose of Patient's Last ARISTADA Injection	Length of Time Since Last Injection		
	No Oral Supplementation Required	Supplement with 7 Days Oral Aripiprazole	Supplement with 21 Days Oral Aripiprazole
Monthly 441 mg	≤ 6 weeks	> 6 and ≤ 7 weeks	> 7 weeks
Monthly 662 mg	≤ 8 weeks	> 8 and ≤ 12 weeks	> 12 weeks
Monthly 882 mg	≤ 8 weeks	> 8 and ≤ 12 weeks	> 12 weeks
882 mg every 6 weeks	≤ 8 weeks	> 8 and ≤ 12 weeks	> 12 weeks

[a] The patient should supplement with the same dose of oral aripiprazole as when the patient began ARISTADA (see Table 2).

2.3. Early Dosing

The recommended ARISTADA dosing interval is either monthly for the 441 mg, 662 mg and 882 mg doses or every 6 weeks for 882 mg dose and should be maintained. In the event of early dosing, an ARISTADA injection should not be given earlier than 14 days after the previous injection.

2.4. Dose Adjustments for CYP450 Considerations

Refer to the prescribing information for oral aripiprazole for recommendations regarding dosage adjustments due to drug interactions, for the first 21 days when the patient is taking oral aripiprazole concomitantly with the first dose of ARISTADA.

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Once stabilized on ARISTADA, refer to the dosing recommendations below for patients taking CYP2D6 inhibitors, CYP3A4 inhibitors, or CYP3A4 inducers:

- No dosage changes recommended for ARISTADA, if CYP450 modulators are added for less than 2 weeks.
- Make dose changes to ARISTADA if CYP450 modulators are added for greater than 2 weeks (see Table 4).

Table 4: ARISTADA Dose Adjustments with Concomitant CYP450 Modulator Use

Concomitant Medicine	**Dose Change for ARISTADA**[a]
Strong CYP3A4 Inhibitor	Reduce the dose of ARISTADA to the next lower strength. No dosage adjustment is necessary in patients taking 441 mg ARISTADA, if tolerated. *For patients known to be poor metabolizers of CYP2D6*: Reduce dose to 441 mg from 662 mg or 882 mg. No dosage adjustment is necessary in patients taking 441 mg ARISTADA, if tolerated.
Strong CYP2D6 Inhibitor	Reduce the dose of ARISTADA to the next lower strength. No dosage adjustment is necessary in patients taking 441 mg ARISTADA, if tolerated. *For patients known to be poor metabolizers of CYP2D6*: No dose adjustment required.
Both Strong CYP3A4 Inhibitor and Strong CYP2D6 Inhibitor	Avoid use for patients at 662 mg or 882 mg dose. No dosage adjustment is necessary in patients taking 441 mg ARISTADA, if tolerated.
CYP3A4 Inducers	No dose adjustment for 662 mg and 882 mg dose, increase the 441 mg dose to 662 mg.

[a] For the 882 mg dose administered every 6 weeks, the next lower strength should be 441 mg administered every 4 weeks.

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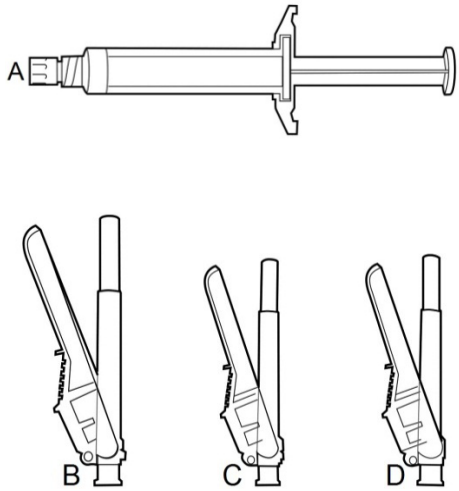
2.5. Instructions for Use

The kit contains a syringe containing ARISTADA sterile aqueous suspension and 2 or 3 safety needles depending on dose (a 2-inch 20 gauge needle with yellow needle hub, a 1 ½-inch 20 gauge needle with yellow needle hub, and a 1-inch 21 gauge needle with green needle hub (441 mg kit only)) for intramuscular injection. All materials should be stored at room temperature.



A | 5 ML SYRINGE containing ARISTADA sterile aqueous suspension

B | 20 GAUGE NEEDLE, 2-INCH with yellow needle hub

C | 20 GAUGE NEEDLE, 1½-INCH with yellow needle hub

D | 21 GAUGE NEEDLE, 1-INCH with green needle hub

1. TAP and **SHAKE** the syringe.

1a. Tap the syringe at least 10 times to dislodge any material which may have settled.

1b. Shake the syringe vigorously for a minimum of 30 seconds to ensure a uniform suspension. If the syringe is not used within 15 minutes, shake again for 30 seconds.

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2. SELECT the injection needle.

2a. Select injection site.

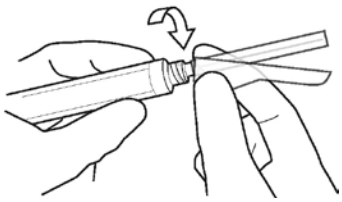
2b. Select needle length based on injection site. For patients with a larger amount of subcutaneous tissue overlaying the injection site muscle, use the longer of the needles provided.

Table 5: Injection Site and Associated Needle Length

INJECTION SITE	NEEDLE LENGTH
441 mg dose	
Deltoid	21 GAUGE, 1-INCH or 20 GAUGE, 1½-INCH
Gluteal	20 GAUGE, 1½-INCH or 20 GAUGE, 2-INCH
662 mg dose	
Gluteal	20 GAUGE, 1½-INCH or 20 GAUGE, 2-INCH
882 mg dose	
Gluteal	20 GAUGE, 1½-INCH or 20 GAUGE, 2-INCH

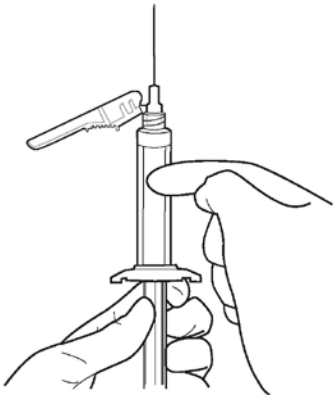
3. ATTACH the injection needle.

Attach the appropriate needle securely with a clockwise twisting motion. Do NOT overtighten. Overtightening could lead to needle hub cracking.

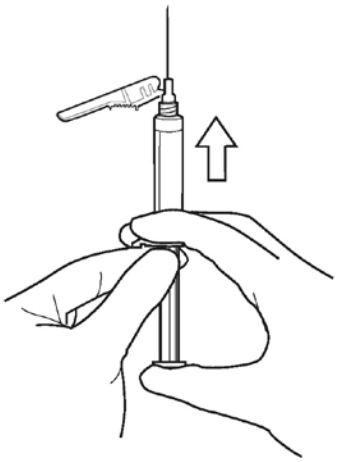


4. PRIME the syringe to remove air.

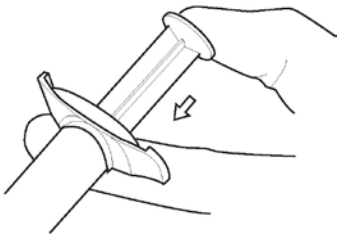
4a. Bring the syringe into upright position and **tap** the syringe to bring air to the top.



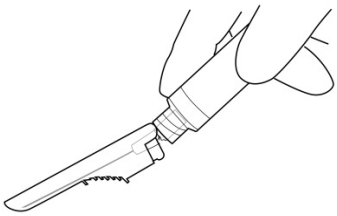
4b. Remove air by depressing the plunger rod. A few drops of suspension will be released.



5. ADMINISTER the entire content intramuscularly. Do not inject by any other route. Inject in a rapid and continuous manner (less than 10 seconds).



6. DISPOSE of the needle. Cover the needle by pressing the safety device. Dispose of used and unused items in a proper waste container.



3. DOSAGE FORMS AND STRENGTHS

ARISTADA is a white to off-white aqueous extended-release suspension provided in a single-use pre-filled syringe for intramuscular injection in the deltoid or gluteal muscle at the 441 mg dose strength and in the gluteal muscle at dose strengths of 662 mg and 882 mg.

ARISTADA is available as described in Table 6.

Table 6: Presentations of ARISTADA

Dose Strength	Volume	Inject Intramuscularly	Color Label
441 mg	1.6 mL	Deltoid or Gluteal Muscle	Light Blue
662 mg	2.4 mL	Gluteal Muscle Only	Green
882 mg	3.2 mL	Gluteal Muscle Only	Burgundy

4. CONTRAINDICATIONS

ARISTADA is contraindicated in patients with a known hypersensitivity reaction to aripiprazole. Hypersensitivity reactions have ranged from pruritus/urticaria to anaphylaxis *[see Adverse Reactions (6)]*.

5. WARNINGS AND PRECAUTIONS

5.1. Increased Mortality in Elderly Patients with Dementia-related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group.

Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. ARISTADA is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning, Warnings and Precautions (5.2)]*.

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5.2. Cerebrovascular Adverse Reactions, Including Stroke

In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly patients with dementia, there was a higher incidence of cerebrovascular adverse reactions (cerebrovascular accidents and transient ischemic attacks) including fatalities compared to placebo-treated patients. ARISTADA is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning, Warnings and Precautions (5.1)]*.

5.3. Neuroleptic Malignant Syndrome

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) may occur in association with antipsychotic drugs, including ARISTADA. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases in which the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

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

If a patient appears to require antipsychotic drug treatment after recovery from NMS, reintroduction of drug therapy should be closely monitored, since recurrences of NMS have been reported.

5.4. 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 predict which patients will 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 appear to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase, but the syndrome can develop after relatively brief treatment periods at low doses, although this is uncommon.

There is no known treatment for established tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment itself may suppress (or partially suppress) the signs and symptoms of the syndrome and may thus

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mask the underlying process. The effect of symptomatic suppression on the long-term course of the syndrome is unknown.

Given these considerations, ARISTADA 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 is known to respond to antipsychotic drugs. 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 treated with ARISTADA drug discontinuation should be considered. However, some patients may require treatment with ARISTADA despite the presence of the syndrome.

5.5. Metabolic Changes

Atypical antipsychotic drugs have been associated with metabolic changes that include hyperglycemia/diabetes mellitus, dyslipidemia, and 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 oral aripiprazole. 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.

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 require continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

In the long-term, open-label schizophrenia study with ARISTADA, 14% of patients with normal hemoglobin A1c (<5.7%) at baseline developed elevated levels (≥5.7%) post-baseline.

Dyslipidemia

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

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In the long-term, open-label schizophrenia study with ARISTADA, shifts in baseline fasting total cholesterol from normal (<200 mg/dL) to high (≥240 mg/dL) were reported in 1% of patients; shifts in baseline fasting LDL cholesterol from normal (<100 mg/dL) to high (≥160 mg/dL) were reported in 1% of patients; and shifts in baseline fasting triglycerides from normal (<150 mg/dL) to high (≥200 mg/dL) were reported in 8% of patients. In the same study, shifts in baseline fasting total cholesterol from borderline (≥ 200 mg/dL and <240 mg/dL) to high (≥240 mg/dL) were reported in 15% of patients; shifts in baseline fasting LDL cholesterol from borderline (≥100 mg/dL and <160 mg/dL) to high (≥160 mg/dL) were reported in 8% of patients; and shifts in baseline fasting triglycerides from borderline (≥150 mg/dL and <200 mg/dL) to high (≥200 mg/dL) were reported in 35% of patients. In addition, the proportion of patients with shifts in fasting HDL cholesterol from normal (≥40 mg/dL) to low (<40 mg/dL) was reported in 15% of patients.

Weight Gain

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

The proportion of adult patients with weight gain ≥7% of body weight is presented in Table 7.

Table 7: Proportion of Adult Patients with Shifts in Weight in the 12-Week, Placebo-Controlled, Fixed-Dose Schizophrenia Trial

		ARISTADA	
	Placebo N = 207 (%)	**441 mg N = 207 (%)**	**882 mg N = 208 (%)**
Weight Gain			
≥7% increase from baseline	6	10	9

5.6. Pathological Gambling and Other Compulsive Behaviors

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

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5.7. Orthostatic Hypotension

Aripiprazole may cause orthostatic hypotension, perhaps due to its α_1-adrenergic receptor antagonism. Associated adverse reactions related to orthostatic hypotension can include dizziness, lightheadedness and tachycardia. Generally, these risks are greatest at the beginning of treatment and during dose escalation. Patients at increased risk of these adverse reactions or at increased risk of developing complications from hypotension include those with dehydration, hypovolemia, treatment with antihypertensive medication, history of cardiovascular disease (e.g., heart failure, myocardial infarction, ischemia, or conduction abnormalities), history of cerebrovascular disease, as well as patients who are antipsychotic-naïve. In such patients, consider using a lower starting dose, and monitor orthostatic vital signs.

Orthostatic hypotension was reported for one patient in the ARISTADA 882 mg group (0.5%) and no patients in the ARISTADA 441 mg and placebo groups in the 12-week schizophrenia efficacy study *[see Clinical Studies (14)]*. In the long-term open-label schizophrenia study, orthostatic hypotension was reported for 1 (0.2%) patient treated with ARISTADA. Orthostatic hypotension was defined as a decrease in systolic blood pressure ≥20 mmHg accompanied by an increase in heart rate ≥25 bpm when comparing standing to supine values.

5.8. Falls

Antipsychotics including ARISTADA may cause somnolence, postural hypotension, or 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 those patients on long-term antipsychotic therapy.

5.9. Leukopenia, Neutropenia, and Agranulocytosis

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

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC)/absolute neutrophil count (ANC) and history of drug-induced leukopenia/neutropenia. In patients with a history of a clinically significant low WBC/ANC or drug-induced leukopenia/neutropenia, perform a complete blood count (CBC) frequently during the first few months of therapy. In such patients, consider discontinuation of ARISTADA at the first sign of a clinical 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 ARISTADA in patients with severe neutropenia (absolute neutrophil count $<1000/mm^3$) and follow their WBC until recovery.

5.10. Seizures

As with other antipsychotic drugs, use ARISTADA cautiously in patients with a history of seizures or with conditions that lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

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5.11. Potential for Cognitive and Motor Impairment

ARISTADA, like other antipsychotics, has 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 therapy with ARISTADA does not affect them adversely.

5.12. Body Temperature Regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing ARISTADA 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).

5.13. Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. ARISTADA and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

6. ADVERSE REACTIONS

The following are discussed in more details in other sections of the labeling:

- Increased Mortality in Elderly Patients with Dementia-related Psychosis *[see Boxed Warning, Warnings and Precautions (5.1)]*
- Cerebrovascular Adverse Reactions, Including Stroke *[see Boxed Warning, Warnings and Precautions (5.2)]*
- Neuroleptic Malignant Syndrome *[see Warnings and Precautions (5.3)]*
- Tardive Dyskinesia *[see Warnings and Precautions (5.4)]*
- Metabolic Changes *[see Warnings and Precautions (5.5)]*
- Pathological Gambling and Other Compulsive Behaviors *[see Warnings and Precautions (5.6)]*
- Orthostatic Hypotension *[see Warnings and Precautions (5.7)]*
- Falls *[see Warnings and Precautions (5.8)]*
- Leukopenia, Neutropenia, and Agranulocytosis *[see Warnings and Precautions (5.9)]*
- Seizures *[see Warnings and Precautions (5.10)]*
- Potential for Cognitive and Motor Impairment *[see Warnings and Precautions (5.11)]*
- Body Temperature Regulation *[see Warnings and Precautions (5.12)]*
- Dysphagia *[see Warnings and Precautions (5.13)]*

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6.1. Clinical Studies 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.

ARISTADA

Patient Exposure

ARISTADA has been evaluated for safety in 880 adult patients in clinical trials in schizophrenia.

Commonly Observed Adverse Reactions

The most common adverse reaction (incidence ≥5% and at least twice the rate of placebo in patients treated with ARISTADA) was akathisia.

Adverse Reactions Occurring at an Incidence of 2% or More in ARISTADA-Treated Patients

Adverse reactions associated with the use of ARISTADA (incidence of 2% or greater, rounded to the nearest percent and ARISTADA incidence greater than placebo) that occurred are shown in Table 8.

Table 8: Adverse Reaction in 2% or More of ARISTADA-Treated Patients and That Occurred at Greater Incidence than in the Placebo-Treated Patients in the 12-Week, Placebo-Controlled, Fixed-Dose Schizophrenia Trial

Adverse Reaction System Organ Class Preferred Term	Placebo N=207 (%)	Aripiprazole Lauroxil 441 mg N=207 (%)	Aripiprazole Lauroxil 882 mg N=208 (%)
General disorders and administration site conditions			
Injection site pain	2	3	4
Investigations			
Increased weight	1	2	2
Increased blood creatine phosphokinase	0	2	1
Nervous system disorders			
Akathisia	4	11	11
Headache	3	3	5
Psychiatric disorders			
Insomnia	2	3	4
Restlessness	1	3	1

Injection Site Reactions

Injection site reactions were reported by 4% of patients treated with 441 mg ARISTADA and 5% of patients treated with 882 mg ARISTADA compared to 2% of patients treated with placebo. Most of these were injection site pain (3%, 4% and 2% in the 441 mg ARISTADA, 882 mg

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ARISTADA and placebo groups, respectively) and most were associated with the first injection, and decreased with each subsequent injection to less than or equal to 1% for both doses of ARISTADA and placebo. Other injection site reactions (induration, swelling and redness) occurred at less than 1%.

Extrapyramidal Symptoms

In the 12-week schizophrenia efficacy study *[see Clinical Studies (14)]*, for ARISTADA-treated patients, the incidence of other EPS-related events, excluding akathisia and restlessness, was 5% and 7% for patients on 441 mg and 882 mg, respectively, versus 4% for placebo-treated patient (Table 9).

Table 9: Incidence of EPS Compared to Placebo

Adverse Reaction Term	Placebo N=207 (%)	ARISTADA 441 mg N=207 (%)	ARISTADA 882 mg N=208 (%)
Akathisia	4	11	11
Restlessness	1	3	1
Other EPS	4	5	7
Dystonia	1	2	2
Parkinsonism	3	3	4

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.

Other Adverse Reactions Observed in Clinical Studies

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.

Cardiac – angina pectoris, tachycardia, palpitations

Gastrointestinal disorders – constipation, dry mouth

General disorders – asthenia

Musculoskeletal – muscular weakness

Nervous system disorders – dizziness

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Psychiatric disorders – anxiety, suicide

Adverse Reactions Reported in Clinical Trials with Oral Aripiprazole

The following is a list of additional adverse reactions that have been reported in clinical trials with oral aripiprazole and not reported above for ARISTADA.

Blood and Lymphatic System Disorders: thrombocytopenia

Cardiac Disorders: bradycardia, atrial flutter, cardiorespiratory arrest, atrioventricular block, atrial fibrillation, myocardial ischemia, myocardial infarction, cardiopulmonary failure

Eye Disorders: photophobia, diplopia

Gastrointestinal Disorders: gastroesophageal reflux disease

General Disorders and Administration Site Conditions: peripheral edema, chest pain, face edema

Hepatobiliary Disorders: hepatitis, jaundice

Immune System Disorders: hypersensitivity

Injury, Poisoning, and Procedural Complications: fall, heat stroke

Investigations: weight decreased, hepatic enzyme increased, blood glucose increased, blood lactate dehydrogenase increased, gamma glutamyl transferase increased, blood prolactin increased, blood urea increased, blood creatinine increased, blood bilirubin increased, electrocardiogram QT prolonged, glycosylated hemoglobin increased

Metabolism and Nutrition Disorders: anorexia, hypokalemia, hyponatremia, hypoglycemia

Musculoskeletal and Connective Tissue Disorders: muscle tightness, rhabdomyolysis, mobility decreased

Nervous System Disorders: memory impairment, cogwheel rigidity, hypokinesia, myoclonus, bradykinesia, akinesia, myoclonus, coordination abnormal, speech disorder, choreoathetosis

Psychiatric Disorders: aggression, loss of libido, delirium, libido increased, anorgasmia, tic, homicidal ideation, catatonia, sleep walking

Renal and Urinary Disorders: urinary retention, nocturia

Reproductive System and Breast Disorders: erectile dysfunction, gynaecomastia, menstruation irregular, amenorrhea, breast pain, priapism

Respiratory, Thoracic, and Mediastinal Disorders: nasal congestion, dyspnea

Skin and Subcutaneous Tissue Disorders: rash, hyperhidrosis, pruritus, photosensitivity reaction, alopecia, urticaria

Vascular Disorders: hypotension, hypertension

6.2. Postmarketing Experience

The following adverse reactions have been identified during post-approval use of oral aripiprazole. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or to establish a causal relationship to drug exposure: occurrences of allergic reaction (anaphylactic reaction, angioedema,

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laryngospasm, pruritus/urticaria, or oropharyngeal spasm), pathological gambling, hiccups and blood glucose fluctuation.

7. DRUG INTERACTIONS

7.1. Drugs Having Clinically Important Interactions with ARISTADA

Table 10: Clinically Important Drug Interactions with ARISTADA

Concomitant Drug Name or Drug Class	Clinical Rationale	Clinical Recommendation
Strong CYP3A4 Inhibitors (e.g., itraconazole, clarithromycin) or strong CYP2D6 inhibitors (e.g., quinidine, fluoxetine, paroxetine)	The concomitant use of oral aripiprazole with strong CYP3A4 or CYP2D6 inhibitors increased the exposure of aripiprazole compared to the use of oral aripiprazole alone *[see Clinical Pharmacology (12.3)]*.	With concomitant use of ARISTADA with a strong CYP3A4 inhibitor or CYP2D6 inhibitor for more than 2 weeks reduce the ARISTADA dose *[see Dosage and Administration (2.4)]*.
Strong CYP3A4 Inducer (e.g., carbamazepine, rifampin)	The concomitant use of oral aripiprazole and carbamazepine decreased the exposure of aripiprazole compared to the use of oral aripiprazole alone *[see Clinical Pharmacology (12.3)]*.	With concomitant use of ARISTADA with a strong CYP3A4 inducer for more than 2 weeks consider increasing the ARISTADA dose *[see Dosage and Administration (2.4)]*.
Antihypertensive Drugs	Due its alpha adrenergic antagonism, aripiprazole has the potential to enhance the effect of certain antihypertensive agents.	Monitor blood pressure and adjust dose accordingly *[see Warnings and Precautions (5.7)]*.
Benzodiazepines (e.g., lorazepam)	The intensity of sedation was greater with the combination of oral aripiprazole and lorazepam as compared to that observed with aripiprazole alone. The orthostatic hypotension observed was greater with the combination as compared to that observed with lorazepam alone *[see Warnings and Precautions (5.7)]*.	Monitor sedation and blood pressure. Adjust dose accordingly.

7.2. Drugs Having No Clinically Important Interactions with ARISTADA

Based on pharmacokinetic studies with oral aripiprazole, no dosage adjustment of ARISTADA is required when administered concomitantly with famotidine, valproate, lithium *[see Clinical Pharmacology (12.3)]*.

In addition, no dosage adjustment is necessary for substrates of CYP2D6 (e.g., dextromethorphan, fluoxetine, paroxetine, or venlafaxine), CYP2C9 (e.g., warfarin), CYP2C19 (e.g., omeprazole, warfarin, escitalopram), or CYP3A4 (e.g., dextromethorphan) when

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co-administered with ARISTADA. Additionally, no dosage adjustment is necessary for valproate, lithium, lamotrigine, or sertraline when co-administered with ARISTADA *[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 ARISTADA during pregnancy. For more information, contact the National Pregnancy Registry for Atypical Antipsychotics at 1-866-961-2388 or visit http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/ .

Risk Summary

Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. Limited published data on aripiprazole use in pregnant women are not sufficient to inform any drug-associated risks for birth defects or miscarriage. No teratogenicity was observed in animal reproductive studies with intramuscular administration of aripiprazole lauroxil to rats and rabbits during organogenesis at doses up to 6 and 18 times, respectively, the maximum recommended human dose (MRHD) of 882 mg based on body surface area (mg/m^2). However, aripiprazole caused developmental toxicity and possible teratogenic effects in rats and rabbits *[see Data]*. The background risk of major birth defects and miscarriage for the indicated population are unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively. Advise pregnant women of the potential risk to a fetus.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Extrapyramidal and/or withdrawal symptoms, including agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder have been reported in neonates who were exposed to antipsychotic drugs 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 recover within hours or days without specific treatment; others required prolonged hospitalization.

Data

Animal Data for Aripiprazole Lauroxil

Aripiprazole lauroxil did not cause adverse developmental or maternal effects in rats or rabbits when administered intramuscularly during the period of organogenesis at doses of 18, 49, or 144 mg/animal in pregnant rats which are approximately 0.7 to 6 times the maximum recommended human dose (MRHD) of 882 mg on mg/m^2 basis, and at doses of 241, 723, and 2893 mg/animal in pregnant rabbits which are approximately 1 to 18 times the MRHD on mg/m^2

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basis. However, aripiprazole caused developmental toxicity and possible teratogenic effects in rats and rabbits *[see Data below]*.

Animal Data for Aripiprazole

Pregnant rats were treated with oral doses of 3, 10, and 30 mg/kg/day which are approximately 1 to 10 times the oral maximum recommended human dose [MRHD] of 30 mg/day on mg/m^2 basis of aripiprazole during the period of organogenesis. Treatment at the highest dose caused a slight prolongation of gestation and delay in fetal development, as evidenced by decreased fetal weight, and undescended testes. Delayed skeletal ossification was observed at 3 and 10 times the oral MRHD on mg/m^2 basis.

At 3 and 10 times the oral MRHD on mg/m^2 basis, delivered offspring had decreased body weights. Increased incidences of hepatodiaphragmatic nodules and diaphragmatic hernia were observed in offspring from the highest dose group (the other dose groups were not examined for these findings). A low incidence of diaphragmatic hernia was also seen in the fetuses exposed to the highest dose. Postnatally, delayed vaginal opening was seen at 3 and 10 times the oral MRHD on mg/m^2 basis and impaired reproductive performance (decreased fertility rate, corpora lutea, implants, live fetuses, and increased post-implantation loss, likely mediated through effects on female offspring) along with some maternal toxicity were seen at the highest dose; however, there was no evidence to suggest that these developmental effects were secondary to maternal toxicity.

In pregnant rabbits treated with oral doses of 10, 30, and 100 mg/kg/day which are 2 to 11 times human exposure at the oral MRHD based on AUC and 6 to 65 times the oral MRHD on mg/m^2 basis of aripiprazole during the period of organogenesis decreased maternal food consumption and increased abortions were seen at the highest dose as well as increased fetal mortality. Decreased fetal weight and increased incidence of fused sternebrae were observed at 3 and 11 times the oral MRHD based on AUC.

In rats treated with oral doses of 3, 10, and 30 mg/kg/day which are 1 to 10 times the oral MRHD on mg/m^2 basis of aripiprazole perinatally and postnatally (from day 17 of gestation through day 21 postpartum), slight maternal toxicity and slightly prolonged gestation were seen at the highest dose. An increase in stillbirths and decreases in pup weight (persisting into adulthood) and survival were also seen at this dose.

8.2. Lactation

Risk Summary

Aripiprazole is present in human breast milk; however, there are insufficient data to assess the amount in human milk, the effects on the breastfed infant, or the effects on milk production. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for ARISTADA and any potential adverse effects on the breastfed infant from ARISTADA or from the underlying maternal condition.

8.4. Pediatric Use

Safety and effectiveness of ARISTADA in patients <18 years of age have not been evaluated.

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8.5. Geriatric Use

Safety and effectiveness of ARISTADA in patients >65 years of age have not been evaluated.

8.6. CYP2D6 Poor Metabolizers

Dosage adjustment is recommended in known CYP2D6 poor metabolizers due to high aripiprazole concentrations. Approximately 8% of Caucasians and 3-8% of Black/African Americans cannot metabolize CYP2D6 substrates and are classified as poor metabolizers (PM) *[see Dosage and Administration (2.4), Clinical Pharmacology (12.3)]*.

8.7. Hepatic and Renal Impairment

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

10. OVERDOSAGE

10.1. Human Experience

The largest known case of acute ingestion with a known outcome involved 1260 mg of oral aripiprazole (42 times the maximum recommended daily dose) in a patient who fully recovered.

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

10.2. Management of Overdosage

In case of overdosage, call the Poison control center immediately at 1-800-222-1222.

11. DESCRIPTION

ARISTADA (aripiprazole lauroxil) is an atypical antipsychotic.

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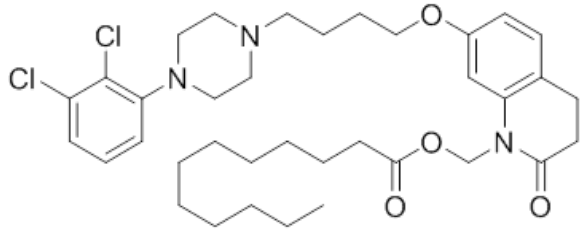
The chemical name of ARISTADA is 7-{4-[4-(2,3-dichlorophenyl)-piperazin-1-yl]butoxy}-2-oxo-3,4-dihydro-2H-quinolin-1-yl)methyl dodecanoate. The empirical formula is $C_{36}H_{51}C_{l2}N_3O_4$ and its molecular weight is 660.7 g/mol. The chemical structure is:



ARISTADA is available as a white to off-white sterile aqueous extended-release suspension for intramuscular injection in the following strengths of aripiprazole lauroxil (and deliverable volumes from a single-use pre-filled syringe): 441 mg (1.6 mL), 662 mg (2.4 mL) and 882 mg (3.2 mL). The inactive ingredients include sorbitan monolaurate (3.8 mg/mL), polysorbate 20 (1.5 mg/mL), sodium chloride (6.1 mg/mL), sodium phosphate dibasic anhydrous, sodium phosphate monobasic and water for injection.

12. CLINICAL PHARMACOLOGY

12.1. Mechanism of Action

ARISTADA is a prodrug of aripiprazole. Following intramuscular injection, ARISTADA is likely converted by enzyme-mediated hydrolysis to N-hydroxymethyl aripiprazole, which is then hydrolyzed to aripiprazole. The mechanism of action of aripiprazole in the body is unknown. However, efficacy could be mediated through a combination of partial agonist activity D_2 and 5-HT_{1A} receptors and antagonist activity at 5-HT_{2A} receptors. Actions at receptors other than D_2, 5-HT_{1A}, and 5-HT_{2A} could explain some of the adverse reactions of aripiprazole (e.g., the orthostatic hypotension observed with aripiprazole may be explained by its antagonist activity at adrenergic $alpha_1$ receptors).

12.2. Pharmacodynamics

Aripiprazole exhibits high affinity for dopamine D_2 and D_3, serotonin 5-HT_{1A} and 5-HT_{2A} receptors (K_i values 0.34 nM, 0.8 nM, 1.7 nM, and 3.4 nM, respectively), moderate affinity for dopamine D_4, serotonin 5-HT_{2C} and 5-HT_7, $alpha_1$-adrenergic and histamine H_1 receptors (K_i values 44 nM, 15 nM, 39 nM, 57 nM, and 61 nM, respectively), and moderate affinity for the serotonin reuptake site (K_i =98 nM). Aripiprazole has no appreciable affinity for cholinergic muscarinic receptors (IC_{50}>1000 nM). Aripiprazole functions as a partial agonist at the dopamine D_2 and the serotonin 5-HT_{1A} receptors, and as an antagonist at serotonin 5-HT_{2A} receptor.

12.3. Pharmacokinetics

ARISTADA is a prodrug of aripiprazole and its activity in the body is primarily due to aripiprazole, and to a lesser extent dehydro-aripiprazole (major metabolite of aripiprazole), which has been shown to have affinities for D_2 receptors similar to aripiprazole and represents 30-40% of the aripiprazole exposure in plasma.

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Absorption and Distribution

After single intramuscular injection the appearance of aripiprazole in the systemic circulation starts from 5 to 6 days and continues to be released for an additional 36 days. Aripiprazole concentrations increase with consecutive doses of ARISTADA and reach steady-state following the fourth monthly injection. The concentration-time course of dehydro-aripiprazole followed that of aripiprazole.

With the addition of oral aripiprazole supplementation for 21 days at the time of the first ARISTADA dose, aripiprazole concentrations reach therapeutic levels within 4 days.

Based on population pharmacokinetic analysis, the apparent volume of distribution of aripiprazole following intramuscular injection of ARISTADA was 268 L, indicating extensive extravascular distribution following absorption. At therapeutic concentrations, aripiprazole and its major metabolite are greater than 99% bound to serum proteins, primarily to albumin. In healthy human volunteers administered 0.5 mg/day to 30 mg/day oral aripiprazole for 14 days, there was dose-dependent D_2 receptor occupancy indicating brain penetration of aripiprazole in humans.

Aripiprazole exposure was similar for deltoid and gluteal intramuscular injections of 441 mg ARISTADA, thus are interchangeable.

Administration of 882 mg every 6 weeks results in plasma aripiprazole concentrations that are within the established therapeutic range for 441 to 882 mg monthly.

Metabolism and Elimination

The biotransformation of ARISTADA likely involves enzyme-mediated hydrolysis to form N-hydroxymethyl-aripiprazole, which subsequently undergoes water mediated hydrolysis to aripiprazole. Elimination of aripiprazole is mainly through hepatic metabolism involving CYP3A4 and CYP2D6. Dosage adjustments are recommended in CYP2D6 poor metabolizers due to high aripiprazole concentrations *[see Dosage and Administration (2.4)]*.

The mean aripiprazole terminal elimination half-life ranged from 29.2 days to 34.9 days after every 4-week injection of ARISTADA 441, 662 and 882 mg. The significantly longer aripiprazole apparent half-life compared to oral aripiprazole (mean 75 hours) is attributed to the dissolution and formation rate-limited elimination of aripiprazole following ARISTADA administration.

Drug Interaction Studies

No specific drug interaction studies have been performed with ARISTADA. The drug interaction data provided below is obtained from studies with oral aripiprazole.

Effects of other drugs on the exposures of aripiprazole and dehydro-aripiprazole are summarized in Figure 1 and Figure 2, respectively. Based on simulation, a 4.5-fold increase in mean C_{max} and AUC values at steady-state is expected when extensive metabolizers of CYP2D6 are administered with both strong CYP2D6 and CYP3A4 inhibitors. After oral administration, a 3-fold increase in mean C_{max} and AUC values at steady-state is expected in poor metabolizers of CYP2D6 administered with strong CYP3A4 inhibitors.

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Figure 1: The Effects of Other Drugs on Aripiprazole Pharmacokinetics

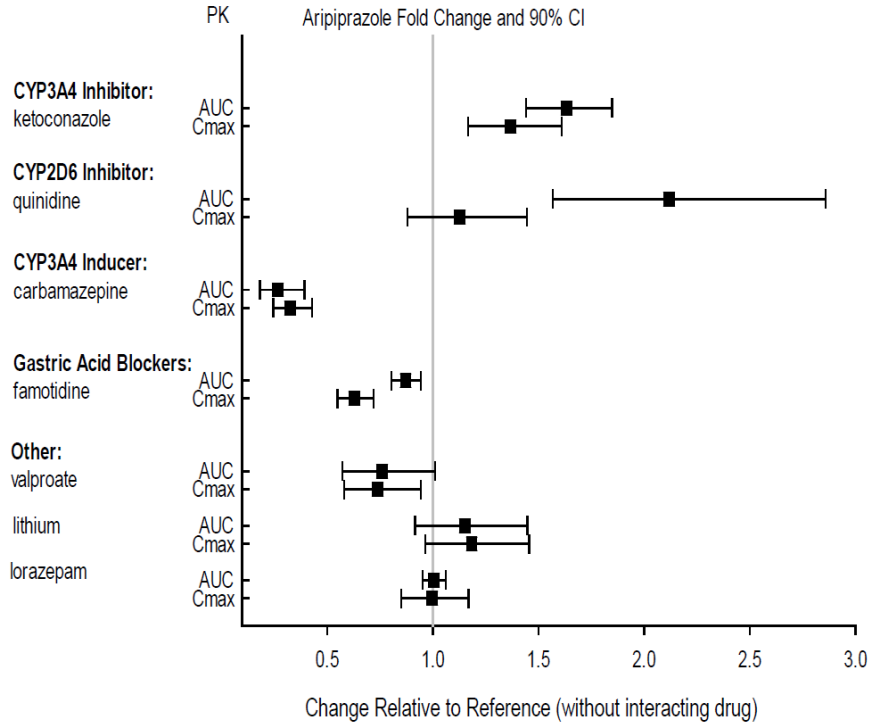
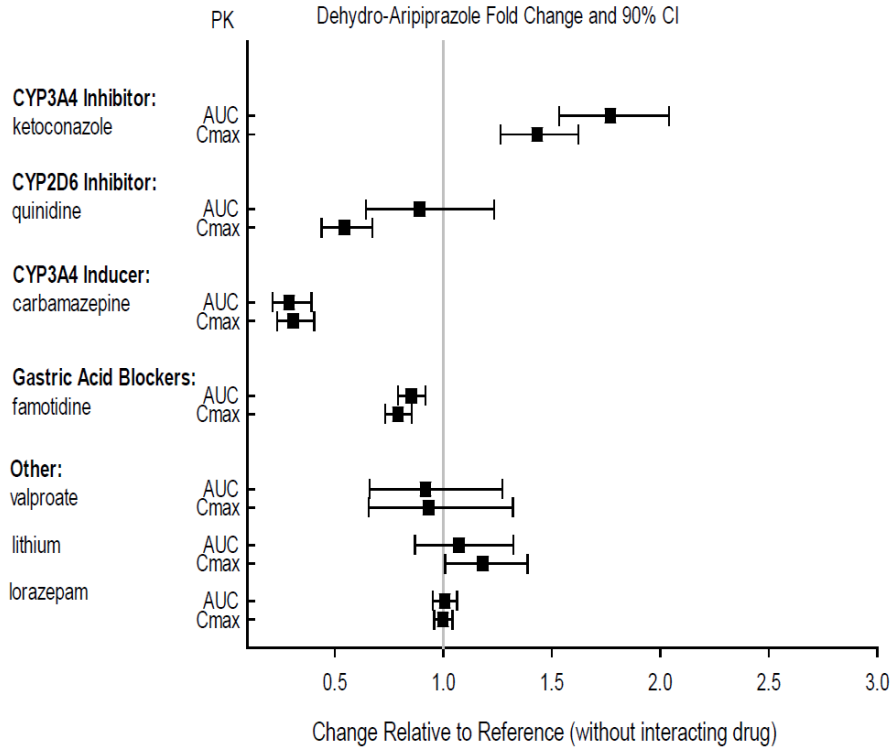


Figure 2: The Effects of Other Drugs on Dehydro-aripiprazole Pharmacokinetics



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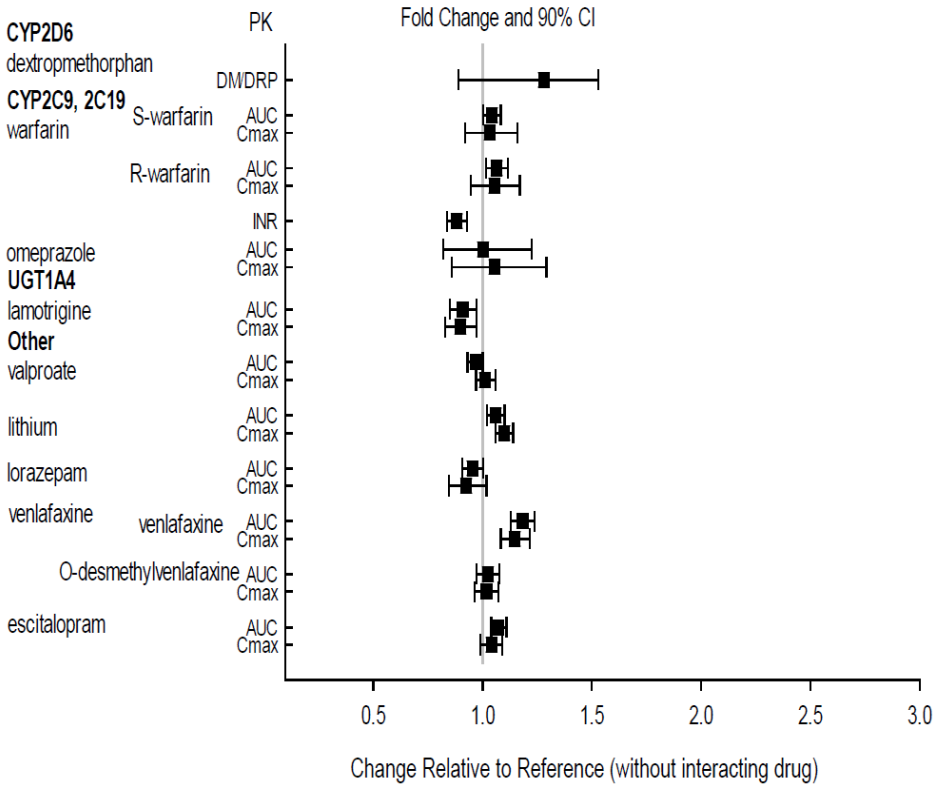
The effects of aripiprazole on the exposures of other drugs are summarized in Figure 3.

Figure 3: The Effects of Oral Aripiprazole on Pharmacokinetics of Other Drugs



Specific Population Studies

A population pharmacokinetic analysis showed no effect of sex, race or smoking on ARISTADA pharmacokinetics *[see Use in Specific Populations (8.8)]*.

Exposures of aripiprazole and dehydro-aripiprazole using oral aripiprazole in specific populations are summarized in Figure 4 and Figure 5, respectively.

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Figure 4: Effects of Intrinsic Factors on Aripiprazole Pharmacokinetics

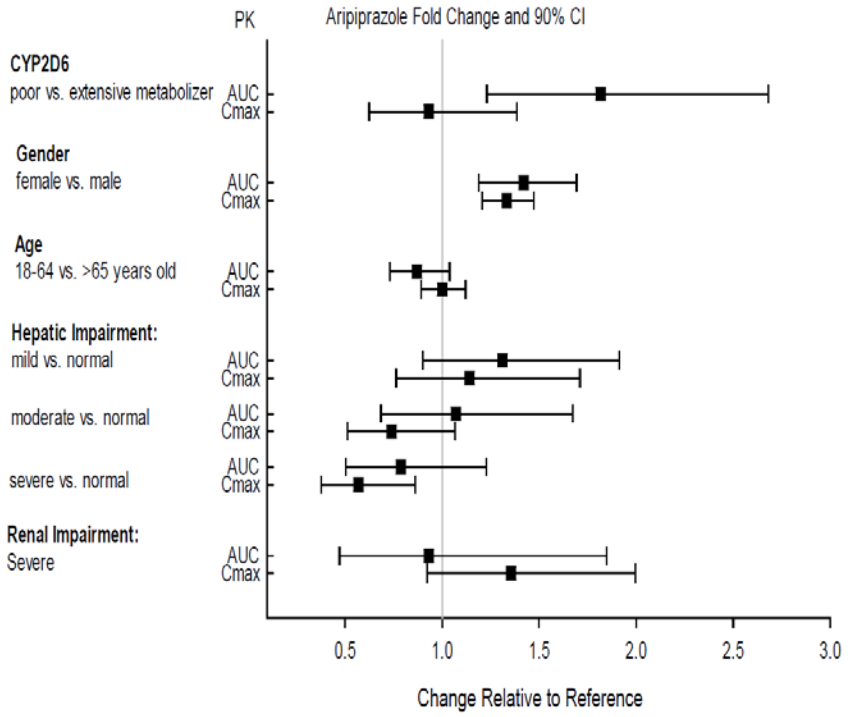
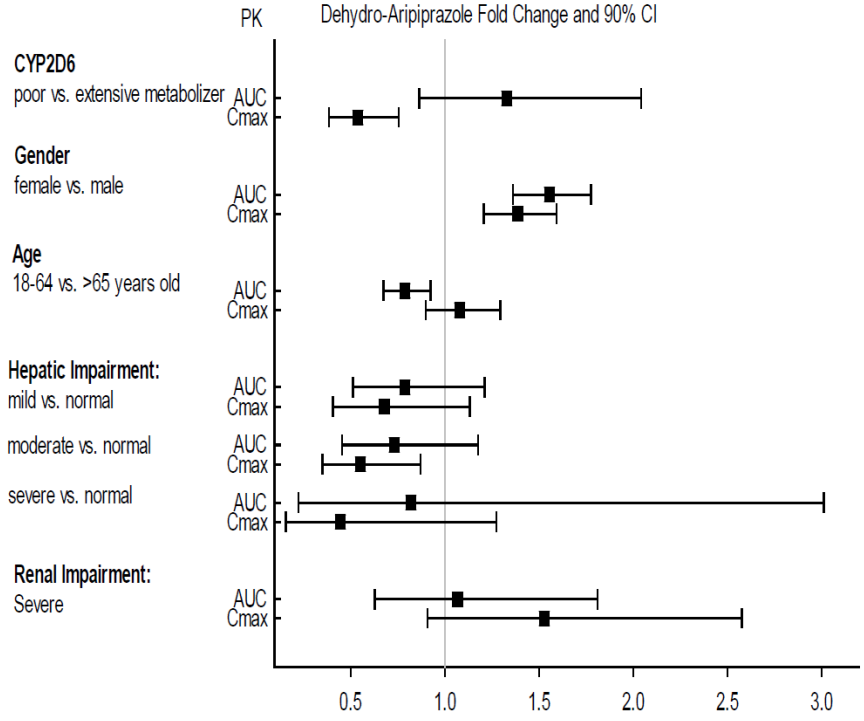


Figure 5: Effects of Intrinsic Factors on Dehydro-aripiprazole Pharmacokinetics



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13. NONCLINICAL TOXICOLOGY

13.1. Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Lifetime carcinogenicity studies have not been conducted with aripiprazole lauroxil.

Lifetime carcinogenicity studies with oral aripiprazole have been conducted in ICR mice and in Sprague-Dawley (SD) and F344 rats. Aripiprazole was administered for 2 years in the diet at doses of 1, 3, 10, and 30 mg/kg/day to ICR mice and 1, 3, and 10 mg/kg/day to F344 rats (0.2 to 5 times and 0.3 to 3 times the oral maximum recommended human dose [MRHD] of 30 mg/day based on mg/m^2, respectively). In addition, SD rats were dosed orally for 2 years at 10, 20, 40, and 60 mg/kg/day (3 to 19 times the oral MRHD based on mg/m^2). Aripiprazole did not induce tumors in male mice or rats. In female mice, the incidences of pituitary gland adenomas and mammary gland adenocarcinomas and adenoacanthomas were increased at dietary doses which are 0.1 to 0.9 times human exposure at the oral MRHD based on AUC and 0.5 to 5 times the oral MRHD on mg/m^2 basis. In female rats, the incidence of mammary gland fibroadenomas was increased at a dietary dose which is 0.1 times human exposure at the oral MRHD based on AUC and 3 times the oral MRHD on mg/m^2 basis; and the incidences of adrenocortical carcinomas and combined adrenocortical adenomas/carcinomas were increased at an oral dose which is 14 times human exposure at oral MRHD based on AUC and 19 times the oral MRHD on mg/m^2 basis.

Proliferative changes in the pituitary and mammary gland of rodents have been observed following chronic administration of other antipsychotic agents and are considered prolactin-mediated. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown.

Mutagenesis

Aripiprazole lauroxil was not mutagenic in the in vitro bacterial reverse mutation assay or clastogenic in the in vitro chromosome aberration assay in human peripheral blood lymphocytes.

Aripiprazole and its metabolite (2,3-DCPP) were clastogenic in the in vitro chromosome aberration assay in Chinese hamster lung (CHL) cells both in the presence and absence of metabolic activation. The metabolite, 2,3-DCPP, produced increases in numerical aberrations in the in vitro assay in CHL cells in the absence of metabolic activation. A positive response was obtained in the oral in vivo micronucleus assay in mice; however, the response was due to a mechanism not considered relevant to humans.

Impairment of Fertility

Animal Data for Aripiprazole Lauroxil

In a rat fertility study, aripiprazole lauroxil was administered intramuscularly. Males were treated with doses of 18, 49, or 144 mg /animal, which are approximately 0.5 to 4 times the maximum recommended human dose [MRHD] of 882 mg on mg/m^2 basis, on Days 1, 21, and 42 prior to and through mating; females were treated at these doses, which are approximately 0.7 to 6 times the MRHD on mg/m^2 basis, once 14 days prior to mating.

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In females, persistent diestrus was observed at all doses and the mean number of cycles was significantly decreased at the highest dose together with an increase in the copulatory interval (delay in mating). Additional changes at the high dose included slight increases in corpora lutea and pre-implantation loss, decline in mating, fertility, and fecundity indices in females and lower mating and fertility indices in males.

Animal Data for Aripiprazole

Female rats were treated with oral aripiprazole doses of 2, 6, and 20 mg/kg/day, which are 0.6 to 6 times the oral maximum recommended human dose [MRHD] of 30 mg/day on mg/m^2 basis, from 2 weeks prior to mating through day 7 of gestation. Estrous cycle irregularities and increased corpora lutea were seen at all doses, but no impairment of fertility was observed. Increased pre-implantation loss was found at 2 and 6 times the oral MRHD on mg/m^2 basis and decreased fetal weight was noted at the highest dose which is 6 times the oral MRHD on mg/m^2 basis.

Male rats were treated with oral aripiprazole doses of 20, 40, and 60 mg/kg/day, which are 6 to 19 times the oral MRHD on mg/m^2 basis, from 9 weeks prior to and through mating. Disturbances in spermatogenesis at the highest dose and prostate atrophy at the mid and high doses were noted which are 13 and 19 times the oral MRHD on mg/m^2 basis, but no impairment of fertility was observed.

13.2. Animal Toxicology and/or Pharmacology

Intramuscular administration of aripiprazole lauroxil to rats and dogs was associated with injection site tissue reactions at all doses in rats treated up to 6 months at doses of 15, 29, and 103 mg/animal (which are approximately 0.3 to 2 times and 0.5 to 4 times the maximum recommended human dose [MRHD] of 882 mg on mg/m^2 basis in males and females, respectively) and in dogs treated up to 9 months at doses of 147, 662, and 2058 mg/animal (which are approximately 0.5 to 8 times and 0.7 to 10 times the MRHD in males and females, respectively on mg/m^2 basis). These injection site tissue reactions consisted of localized granulomatous inflammation and granuloma formation. Transiently impaired limb function and swelling occurred in dogs. The granulomas did not completely resolve 2 months following the last injection in the 6 month rat study and 4 months following the last injection in the 9 month dog study (the low dose groups were not examined for reversibility in these studies).

Orally administered aripiprazole produced retinal degeneration in albino rats in a 26-week chronic toxicity study at a dose of 60 mg/kg, which is 19 times the oral MRHD of 30 mg/day on mg/m^2 basis, and in a 2-year carcinogenicity study at doses of 40 mg/kg and 60 mg/kg, which are 13 and 19 times the oral MRHD on mg/m^2 basis and 7 to 14 times human exposure at the oral MRHD based on AUC. Evaluation of the retinas of albino mice and of monkeys did not reveal evidence of retinal degeneration. Additional studies to further evaluate the mechanism have not been performed. The relevance of this finding to human risk is unknown.

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14. CLINICAL STUDIES

The efficacy of ARISTADA in the treatment of patients with schizophrenia was established, in part, on the basis of efficacy data from trials with the oral formulation of aripiprazole. In addition, the efficacy of ARISTADA was established in a 12-week, randomized, double-blind, placebo-controlled, fixed-dose study in adult patients with schizophrenia meeting DSM-IV TR criteria [Study 1, n = 622; 207 (ARISTADA 441 mg), 208 (ARISTADA 882 mg), and 207 (placebo)]. After establishing tolerability to oral aripiprazole, patients received oral aripiprazole or placebo daily for the first 3 weeks. The intramuscular (IM) injections were administered on Days 1, 29 and 57.

Efficacy was assessed using Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impression Improvement Scale (CGI-I):

- 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 CGI-I rates improvement in mental illness on a scale of 1 (very much improved) to 7 (very much worse) based on the change from baseline in clinical condition.

Eligible patients were 18 to 70 years of age with PANSS total score of 70 to 120 and a score of ≥4 for at least 2 of the selected Positive Scale items. Patients were also required to have a CGI-S score of ≥4.

The primary efficacy variable was the change from baseline to endpoint (Day 85) in PANSS total score. Statistically significant separation from placebo on PANSS total score change was observed in each ARISTADA dose group (Table 11).

Table 11: Primary Efficacy Results

Study Number	Treatment Group	Primary Efficacy Measure: PANSS Total Score		
		Mean Baseline Score (SD)	LS Mean Change from Baseline (SE)	Placebo-subtracted Difference[a] (95% CI)
Study 1	ARISTADA 441 mg[b]	92.6 (10.2)	-20.9 (1.4)	-10.9 (-14.5, -7.3)
	ARISTADA 882 mg[b]	92.0 (10.8)	-21.8 (1.4)	-11.9 (-15.4, -8.3)
	Placebo	93.9 (11.3)	-9.8 (1.4)	--

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: confidence interval, not adjusted for multiple comparisons.
[a] Difference (drug minus placebo) in least-squares mean change from baseline.
[b] Doses that are demonstrated to be effective.

The visit-wise mean change from baseline on PANSS total score change for each treatment group is shown in Figure 6.

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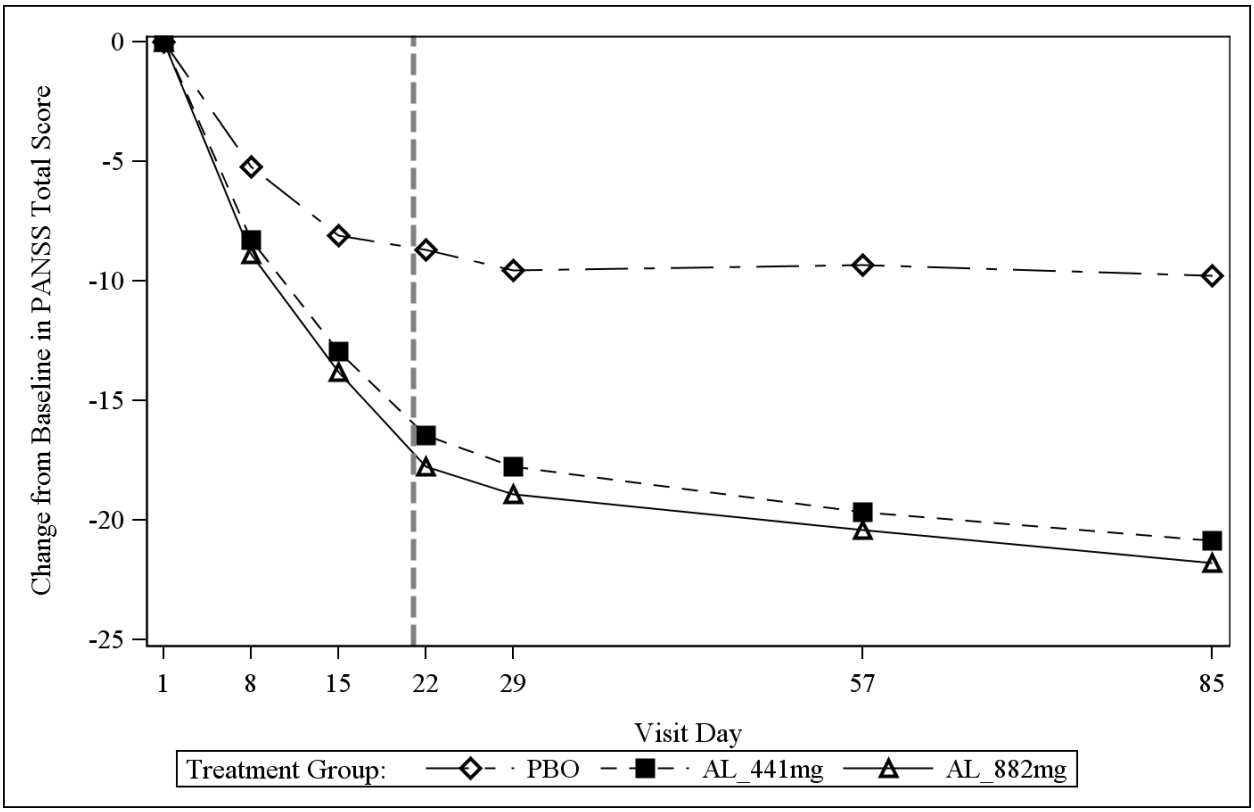
Figure 6: Change from Baseline in PANSS Total Score



Abbreviations: AL= ARISTADA; PBO=placebo; PANSS=Positive and Negative Syndrome Scale.
Vertical dotted line indicates end of oral supplementation.

Subgroup analyses did not suggest any clear evidence of differential responsiveness in treatment outcome as a function of age, gender, race, or weight.

The secondary efficacy endpoint was defined as the CGI-I score at Day 85. Both ARISTADA treatment groups demonstrated statistically significantly better CGI-I scores versus placebo.

16. HOW SUPPLIED/ STORAGE AND HANDLING

16.1. How Supplied

ARISTADA extended-release injectable suspension is available in strengths of 441 mg in 1.6 mL, 662 mg in 2.4 mL, and 882 mg in 3.2 mL. The kit contains a 5-mL pre-filled syringe containing ARISTADA sterile aqueous suspension and safety needles.

- The 441 mg strength kit (NDC 65757-401-03*; light blue label*) contains three safety needles; a 1-inch (25 mm) 21 gauge, a 1½-inch (38 mm) 20 gauge, and a 2-inch (50 mm) 20 gauge needle.
- The 662 mg strength kit (NDC 65757-402-03*; green label*) contains two safety needles; a 1½-inch (38 mm) 20 gauge and a 2-inch (50 mm) 20 gauge needle.

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- The 882 mg strength kit (NDC 65757-403-03*; burgundy label*) contains two safety needles; a 1½-inch (38 mm) 20 gauge and a 2-inch (50 mm) 20 gauge needle.

16.2. Storage

Store at room temperature 20°C to 25°C (68°F to 77°F) with excursions permitted between 15°C and 30°C (between 59°F and 86°F).

17. PATIENT COUNSELING INFORMATION

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

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. In some cases, but not all, the urges were reported to have stopped when the dose was reduced or stopped *[see Warnings and Precautions (5.6)]*.

Neuroleptic Malignant Syndrome

Counsel patients about a potentially fatal adverse reaction referred to as NMS that has been reported in association with administration of antipsychotic drugs. Advise patients to contact a healthcare provider or report to the emergency room if they experience signs or symptoms of NMS *[see Warnings and Precautions (5.3)]*.

Tardive Dyskinesia

Advise patients that abnormal involuntary movements have been associated with administration of antipsychotic drugs. Counsel patients to notify their healthcare provider if they notice any movements which they cannot control in their face, tongue, or other body part *[see Warnings and Precautions (5.4)]*.

Metabolic Changes (Hyperglycemia and Diabetes Mellitus, Dyslipidemia, and Weight Gain)

Educate patients about the risk of metabolic changes, how to recognize symptoms of hyperglycemia and diabetes mellitus, and the need for specific monitoring, including blood glucose, lipids, and weight *[see Warnings and Precautions (5.5)]*.

Orthostatic Hypotension

Educate patients about the risk of orthostatic hypotension (symptoms include feeling dizzy or lightheaded upon standing), particularly at the time of initiating treatment, re-initiating treatment, or increasing the dose *[see Warnings and Precautions (5.7)]*.

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Falls

Advise patients and their caregivers of the possibility that they may experience somnolence, postural hypotension, or motor and sensory instability, which may lead to the risk of falls, particularly in patients with diseases, conditions, or medications that could exacerbate these effects *[see Warnings and Precautions* (5.8)*]*.

Leukopenia/ Neutropenia

Advise patients with a pre-existing low WBC count or a history of drug-induced leucopenia/neutropenia that they should have their CBC monitored while receiving ARISTADA *[see Warnings and Precautions (*5.9 *)]*.

Interference with Cognitive and Motor Performance

Because ARISTADA may have the potential to impair judgment, thinking or motor skills, instruct patients to be cautious about operating hazardous machinery, including automobiles, until they are reasonably certain that ARISTADA therapy does not affect them adversely *[see Warnings and Precautions (5.11)]*.

Heat Exposure and Dehydration

Advise patients regarding appropriate care in avoiding overheating and dehydration *[see Warnings and Precautions (5.12)]*.

Concomitant Medication

Advise patients to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions *[see Drug Interactions (7)]*.

Pregnancy

Advise patients that ARISTADA may cause extrapyramidal and/or withdrawal symptoms in a neonate and to notify their healthcare provider with a known or suspected pregnancy. Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ARISTADA during pregnancy *[see Use in Specific Populations (8.1)]*.

For additional information, visit www.ARISTADA.com or call 1-866-274-7823

Manufactured and marketed by:

Alkermes, Inc.

852 Winter Street

Waltham, MA 02451-1420

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MEDICATION GUIDE
ARISTADA® (air-is-TAH-dah)
(aripiprazole lauroxil)
extended-release injectable suspension, for intramuscular use

What is the most important information I should know about ARISTADA?

Each injection of ARISTADA must be administered by a healthcare professional only.

ARISTADA may cause serious side effects, including:

- **Increased risk of death in elderly people with dementia-related psychosis.** ARISTADA is not for the treatment of people who have lost touch with reality (psychosis) due to confusion and memory loss (dementia).
- **Neuroleptic malignant syndrome (NMS) a serious condition that can lead to death.** Tell your healthcare provider right away if you have some or all of the following symptoms of NMS:
  - High fever
  - Stiff muscles
  - Confusion
  - Sweating
  - Changes in pulse, heart rate, and blood pressure

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

What is ARISTADA?

ARISTADA is a prescription medicine given by injection by a healthcare professional and used to treat schizophrenia.

It is not known if ARISTADA is safe and effective in children under 18 years of age.

Who should not receive ARISTADA?

Do not receive ARISTADA if you are allergic to aripiprazole or any of the ingredients in ARISTADA. See the end of this leaflet for a complete list of ingredients in ARISTADA.

What should I tell my healthcare provider before receiving ARISTADA?

Before you receive ARISTADA, tells your healthcare provider if you:

- have never taken ABILIFY®, ABILIFY MAINTENA® or any aripiprazole product before
- have diabetes or high blood sugar or a family history of diabetes or high blood sugar. Your healthcare provider should check your blood sugar before you start receiving ARISTADA and during your treatment.
- have or had seizures (convulsions)
- have or had low or high blood pressure
- have or had heart problems or a stroke
- have or had a low white blood cell count
- have any other medical problems including problems that may affect you receiving an injection in your buttocks or your arm
- are pregnant or plan to become pregnant. It is not known if ARISTADA will harm your unborn baby.
  - If you become pregnant while taking ARISTADA, 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 visit http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/
- are breastfeeding or plan to breastfeed. ARISTADA can pass into your milk and it is not known if it may harm your baby. Talk to your healthcare provider about the best way to feed your baby if you receive ARISTADA.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

ARISTADA and other medicines may affect each other causing possible serious side effects. ARISTADA may affect the way other medicines work, and other medicines may affect how ARISTADA works.

Your healthcare provider can tell you if it is safe to take ARISTADA with your other medicines. Do not start or stop any medicines while taking ARISTADA without talking to your healthcare provider first.

Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

How should I receive ARISTADA?

- Follow your ARISTADA treatment schedule exactly as your healthcare provider tells you to.
- Each ARISTADA is an injection given in your arm or buttock by your healthcare provider 1 time a month or 1 time every 6 weeks. You may feel a little pain in your arm or buttock during the injection.
- After your first injection of ARISTADA you should continue your current antipsychotic medicine for 21 days.
- You should not miss a dose of ARISTADA. If you miss a dose for some reason, call your healthcare provider right away to discuss what you should do next.

What should I avoid while receiving ARISTADA?

- **Do not** drive a car, operate machinery, or do other dangerous activities until you know how ARISTADA affects you. ARISTADA may make you feel drowsy.
- **Do not** drink alcohol while you receive ARISTADA.
- **Do not** become too hot or dehydrated while you receive ARISTADA.
  - **Do not** exercise too much.
  - In hot weather, stay inside in a cool place if possible.
  - Stay out of the sun.
  - **Do not** wear too much clothing or heavy clothing.
  - Drink plenty of water.

What are the possible side effects of ARISTADA?

ARISTADA may cause serious side effects, including:

- **See** "**What is the most important information I should know about ARISTADA?**"
- **Stroke in elderly people (cardiovascular problems) that can lead to death**
- **Neuroleptic malignant syndrome (NMS**)**:** Tell your healthcare provider right away if you have some or all of the following symptoms: high fever, stiff muscles, confusion, sweating, changes in pulse, heart rate, and blood pressure. These may be symptoms of a rare and serious condition that can lead to death. Call your healthcare provider right away if you have any of these symptoms.
- **Uncontrolled body movements (tardive dyskinesia):** ARISTADA may cause movements that you cannot control in your face, tongue, or other body parts. Tardive dyskinesia may not go away, even if you stop receiving ARISTADA. Tardive dyskinesia may also start after you stop receiving ARISTADA.
- **Problems with your metabolism such as:**
  - **High blood sugar (hyperglycemia):** Increases in blood sugar can happen in some people who take ARISTADA. 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 receiving ARISTADA and during your treatment.

    Call your healthcare provider if you have any of these symptoms of high blood sugar while receiving ARISTADA:
    - Feel very thirsty
    - Feel very hungry
    - Feel sick to your stomach
    - Need to urinate more than usual
    - Feel weak or tired
    - Feel confused, or your breath smells fruity
  - **Increased fat levels (cholesterol and triglycerides) in your blood.**
  - **Weight gain.** You and your healthcare provider should check your weight regularly.
- **Gambling urges and other uncontrollable (compulsive) behaviors**. Some people taking aripiprazole products have had strong urges to gamble. Other strong urges include increased sex drive, spending money (compulsive shopping), binge eating or eating that you cannot control. If you or your family members notice that you are having strong urges, talk to your healthcare provider. These behaviors may go away if your dose of ARISTADA is lowered or stopped.
- **Decreased blood pressure (orthostatic hypotension).** You may feel lightheaded or faint when you rise too quickly from a sitting or lying position.
- **Low white blood cell count**
- **Seizures (convulsions)**
- **Problems controlling your body temperature so that you feel too warm. See "What should I avoid while receiving ARISTADA?"**
- **Difficulty swallowing**

The most common side effects of ARISTADA include feeling like you need to move to stop unpleasant feelings in your legs (restless leg syndrome or akathisia).

Tell your healthcare provider if you have any side effect that bothers you or that does not go away.

These are not all the possible side effects of ARISTADA. For more information, ask your healthcare provider or pharmacist.

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

General information about the safe and effective use of ARISTADA.

This Medication Guide summarizes the most important information about ARISTADA. If you would like more information, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about ARISTADA that is written for health professionals.

For more information, go to www.ARISTADA.com or call 1-866-274-7823.

What are the ingredients in ARISTADA?

Active ingredient: aripiprazole lauroxil

Inactive ingredients: sorbitan monolaurate, polysorbate 20, sodium chloride, sodium phosphate dibasic anhydrous, sodium phosphate monobasic and water for injection

Manufactured and marketed by: Alkermes, Inc. 852 Winter Street Waltham, MA 02451-1420

This Medication Guide has been approved by the U.S. Food and Drug Administration Approved 07/16