# ARISTADA INITIO® and ARISTADA® PRODUCT MONOGRAPH



#### **INDICATION**

ARISTADA INITIO® (aripiprazole lauroxil), in combination with oral aripiprazole, is indicated for the initiation of ARISTADA® (aripiprazole lauroxil) when used for the treatment of schizophrenia in adults.

ARISTADA is indicated for the treatment of schizophrenia in adults.

#### IMPORTANT SAFETY INFORMATION FOR ARISTADA INITIO AND ARISTADA

#### 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 INITIO and ARISTADA are not approved for the treatment of patients with dementia-related psychosis.

**Contraindication:** Known hypersensitivity reaction to aripiprazole. Reactions have ranged from pruritus/urticaria to anaphylaxis.





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## DISEASE DESCRIPTION

#### Epidemiology

Schizophrenia is a chronic and severely disabling disorder that can be characterized by delusions. hallucinations, disorganized thinking (speech), grossly disorganized or catatonic behavior, and negative symptoms.<sup>1,2</sup> The prevalence of schizophrenia is estimated to be less than 1% in the US adult population, affecting approximately 2.4 million Americans.<sup>1,3</sup> Schizophrenia affects men slightly more often than women<sup>4</sup>; the onset of schizophrenia typically occurs earlier in men (age between 10 and 25 years) than in women (age between 25 and 35).5

People with schizophrenia are about 2.5 times more likely to die earlier than the general population, with early death often due to cardiovascular and respiratory problems, cancer, and suicide.<sup>6,7</sup>

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## DISEASE DESCRIPTION, (CONT.)

#### Clinical presentation and diagnosis

Schizophrenia is characterized by a combination of positive, negative, and general psychopathology. Positive symptoms are psychotic behaviors not observed in healthy individuals and include hallucinations, delusions, and thought and movement disorders.<sup>2</sup> In contrast, negative symptoms are associated with disruptions to normal emotions and behaviors, including flat affect, anhedonia, alogia, avolition, and attention.<sup>2</sup>

The disease course of schizophrenia can vary. Some patients experience acute psychotic episodes followed by periods of relative stability while others are chronically ill. Complete remission is very rare.<sup>2</sup> There is heterogeneity across persons with schizophrenia and there can be marked deterioration with impairments in multiple domains of functioning.8

The diagnosis of schizophrenia follows the 6 criteria set forth by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).<sup>2</sup> Some criteria include patients that have experienced at least 2 of the following symptoms: delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, or negative symptoms. At least one of the symptoms must be the presence of delusions, hallucinations, or disorganized speech. Furthermore, social or occupational dysfunction in areas such as work, interpersonal relations, or self-care at levels markedly lower than those achieved prior to onset, must occur over a significant portion of the time since the onset of the disturbance. Continuous signs of the disturbance must persist for at least 6 months, during which the patient must experience at least 1 month of the symptoms listed above (or less if successfully treated).2

In the clinical trials for ARISTADA® (aripiprazole lauroxil), patients were diagnosed using Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for schizophrenia. In updating to DSM-5, the use of subtypes of schizophrenia was eliminated.9 Instead, DSM-5 introduces the use of psychopathological dimensions. These dimensions of illness are to be rated on a scale from 0 to 4 and include the following: delusions, hallucinations, disorganized speech, abnormal psychomotor behavior, and negative symptoms.<sup>2</sup>

The dimensional model has been adopted in order to describe schizophrenia in a clinically useful manner and facilitate measurement-based treatment.9,10





## ARISTADA INITIO OVERVIEW

Generic name, brand name, and therapeutic class<sup>11</sup>

**Generic name:** aripiprazole lauroxil

Brand name: ARISTADA INITIO®

Therapeutic class: Atypical antipsychotic



#### FDA-approved indication and usage

ARISTADA INITIO® (aripiprazole lauroxil), in combination with oral aripiprazole, is indicated for the initiation of ARISTADA® (aripiprazole lauroxil) when used for the treatment of schizophrenia in adults.<sup>11</sup>

U.S. Food and Drug Administration (FDA) approval of ARISTADA INITIO was granted on June 29, 2018.<sup>12</sup>

#### American Hospital Formulary Service (AHFS) or other drug classification

The AHFS classification for atypical antipsychotics is 28:16.08.04.13

#### Product description and clinical pharmacology<sup>11</sup>

ARISTADA INITIO contains aripiprazole lauroxil, an atypical antipsychotic. The chemical name of aripiprazole lauroxil 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  $C_{36}H_{51}Cl_2N_3O_4$  and its molecular weight is 660.7 g/mol. The chemical structure is:

Following intramuscular injection, aripiprazole lauroxil is likely converted by enzyme-mediated hydrolysis to *N*-hydroxymethyl aripiprazole, which is then hydrolyzed to aripiprazole.

ARISTADA INITIO is available as a white to off-white sterile aqueous extended-release suspension for intramuscular injection. It is available in the following strength of aripiprazole lauroxil (and deliverable volume from a single dose pre-filled syringe): 675 mg (2.4 mL). The inactive ingredients include polysorbate 20 (16.2 mg/mL), sodium chloride (3.3 mg/mL), sodium citrate dihydrate (8.1 mg/mL), sodium phosphate dibasic anhydrous, sodium phosphate monobasic, and water for injection.





## ARISTADA OVERVIEW

Generic name, brand name, and therapeutic class<sup>14</sup>

**Generic name:** aripiprazole lauroxil

Brand name: ARISTADA®

Therapeutic class: Atypical antipsychotic



#### FDA-approved indication and usage

ARISTADA® (aripiprazole lauroxil) is an atypical antipsychotic indicated for the treatment of schozophrenia in adults.<sup>14</sup>

U.S. Food and Drug Administration (FDA) approval of ARISTADA was granted on October 5, 2015.15

#### American Hospital Formulary Service (AHFS) or other drug classification

The AHFS classification for atypical antipsychotics is 28:16.08.04.13

#### Product description and clinical pharmacology<sup>14</sup>

ARISTADA contains aripiprazole lauroxil, an atypical antipsychotic. The chemical name of aripiprazole lauroxil 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  $C_{36}H_{51}Cl_2N_3O_4$  and its molecular weight is 660.7 g/mol. The chemical structure is:

Following intramuscular injection, aripiprazole lauroxil is likely converted by enzyme-mediated hydrolysis to N-hydroxymethyl aripiprazole, which is then hydrolyzed to aripiprazole.

ARISTADA is available as a white to off-white sterile aqueous extended-release suspension for intramuscular injection. It is available in the following strengths of aripiprazole lauroxil (and deliverable volumes from a single dose pre-filled syringe): 441 mg (1.6 mL), 662 mg (2.4 mL), 882 mg (3.2 mL), and 1064 mg (3.9 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.





# CLINICAL PHARMACOLOGY FOR ARISTADA INITIO AND ARISTADA

#### Active moiety<sup>16</sup>

The active moiety of ARISTADA INITIO® (aripiprazole lauroxil) and ARISTADA® (aripiprazole lauroxil) is N-hydroxymethyl aripiprazole.

#### Mechanism of action<sup>11,14</sup>

ARISTADA INITIO and ARISTADA are prodrugs of aripiprazole. Following intramuscular injection, ARISTADA INITIO and ARISTADA are likely converted by enzyme-mediated hydrolysis to N-hydroxymethyl aripiprazole, which is then hydrolyzed to aripiprazole. The mechanism of action of aripiprazole in schizophrenia is unknown. However, efficacy could be mediated through a combination of partial agonist activity at dopamine  $D_2$  and serotonin S-H $T_{14}$  receptors and antagonist activity at  $T_{14}$  receptors.

#### LinkeRx® technology17,18

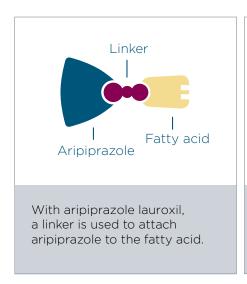
ARISTADA INITIO and ARISTADA utilize the LinkeRx\* technology. LinkeRx\* is proprietary technology used to produce a non-ester prodrug of aripiprazole. Using this system, a linker attaches aripiprazole to a fatty acid tail, creating ARISTADA INITIO and ARISTADA. This covalently bonded modification of aripiprazole is likely converted in vivo by slow dissolution of the drug crystals and subsequent hydrolysis to release aripiprazole.

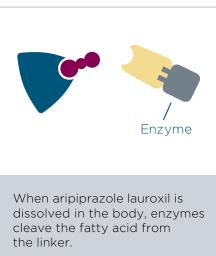
LinkeRx\* technology allows for sustained release with an extended pharmacokinetic profile, regulated absorption, and a low peak-to-trough ratio.

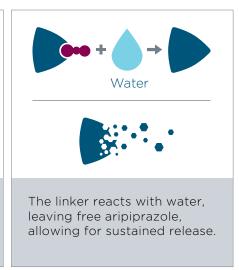
#### Nanocrystal technology<sup>11</sup>

ARISTADA INITIO's specific extended-release and dosing characteristics are derived from aripiprazole lauroxil's submicron particle size distribution.

#### THE BIOTRANSFORMATION OF ARISTADA INITIO AND ARISTADA<sup>17</sup>







Following intramuscular injection, aripiprazole lauroxil is likely converted by enzyme-mediated hydrolysis to an intermediate, which is then hydrolyzed to aripiprazole.

The mechanism of action of aripiprazole in schizophrenia is unknown.<sup>11,14</sup>

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# CLINICAL PHARMACOLOGY FOR ARISTADA INITIO AND ARISTADA, (CONT.)

#### Pharmacodynamics<sup>11,14</sup>

Aripiprazole exhibits high affinity for dopamine  $D_2$  and  $D_3$  ( $K_1$ s 0.34 and 0.8 nM respectively), serotonin 5-HT $_{1A}$  and 5-HT $_{2A}$  receptors ( $K_1$ s 1.7 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 ( $K_1$ s 44 nM, 15 nM, 39 nM, 57 nM, and 61 nM, respectively), and moderate affinity for the serotonin reuptake site ( $K_1$  98 nM). Aripiprazole has no appreciable affinity for cholinergic muscarinic receptors ( $IC_{50} > 1000$  nM). 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, receptors).

#### Pharmacokinetics for ARISTADA INITIO and ARISTADA<sup>11,14</sup>

ARISTADA INITIO® (aripiprazole lauroxil) and ARISTADA® (aripiprazole lauroxil) are prodrugs of aripiprazole and their activity 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.

ARISTADA INITIO and ARISTADA are not interchangeable because of differing pharmacokinetic profiles. ARISTADA INITIO, 30 mg oral aripiprazole, and ARISTADA contribute to systemic aripiprazole exposure at different times throughout treatment initiation.

A pharmacokinetic (PK) bridging study demonstrated that an intramuscular injection of ARISTADA, a 30 mg dose of oral aripiprazole, and a single 675 mg dose of ARISTADA INITIO resulted in aripiprazole concentrations comparable to ARISTADA treatment initiated with 21 days of oral aripiprazole. A single strength of ARISTADA INITIO (i.e., 675 mg) was adequate for all dose levels of oral aripiprazole and ARISTADA.

#### Absorption for ARISTADA INITIO<sup>11</sup>

After single intramuscular injection of ARISTADA INITIO, the appearance of aripiprazole in the systemic circulation occurs on the day of injection; the median time to reach peak plasma exposures is approximately 27 days (range: 16 to 35 days).

With the addition of a single intramuscular injection of ARISTADA INITIO and 30 mg oral aripiparazole at the time of the first ARISTADA dose, aripiprazole concentrations reach relevant levels within 4 days.

Aripiprazole exposure was similar for deltoid and gluteal intramuscular injections of ARISTADA INITIO.

#### Absorption for ARISTADA<sup>14</sup>

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 four months following treatment initiation. The concentration-time course of dehydro-aripiprazole followed that of aripiprazole.

With the addition of a single intramuscular injection of ARISTADA INITIO and 30 mg oral aripiparazole at the time of the first ARISTADA dose, aripiprazole concentrations reach relevant levels within 4 days. Similarly, with the addition of oral aripiprazole supplementation for 21 days at the time of the first ARISTADA dose, aripiprazole concentrations reach relevant levels within 4 days.

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

Administration of 882 mg every 6 weeks or 1064 mg every 2 months results in plasma aripiprazole concentrations that were similar to exposure with 662 mg monthly and are within the range provided by doses of 441 mg monthly and 882 mg monthly. The doses of 441 mg monthly and 882 monthly showed a similar clinical response to each other.

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Please see additional Important Safety Information on pages 38 to 39 and accompanying full Prescribing Information, including Boxed Warning, for ARISTADA INITIO and ARISTADA.

ARISTADA INITIO® aripiprazole lauroxil extended-release injectable suspension



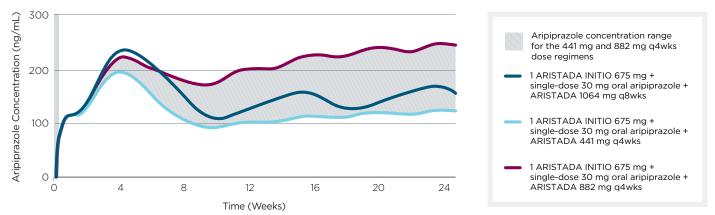
# CLINICAL PHARMACOLOGY FOR ARISTADA INITIO AND ARISTADA, (CONT.)

#### Modeling information for ARISTADA

Modeling showed ARISTADA maintains therapeutic levels of aripiprazole during the dosing period with low peak-to-trough fluctuations.<sup>18</sup>

# MEDIAN SIMULATED ARIPIPRAZOLE PLASMA CONCENTRATIONS FOR THE ARISTADA INITIO REGIMEN® AND ARISTADA 2-MONTH DOSE (1064 MG)<sup>11,19</sup>

Modeling-based simulations of ARISTADA INITIO regimen and ARISTADA 1064 mg q8wks yielded aripiprazole concentrations that fall within the estimated aripiprazole exposure range of the studied approved dose regimens of 441 mg q4wks and 882 mg q4wks.<sup>11,19</sup>



<sup>&</sup>lt;sup>a</sup>The ARISTADA INITIO regimen is defined as a single injection of ARISTADA INITIO (675 mg) given in conjunction with a single 30 mg dose of oral aripiprazole."

#### Distribution for ARISTADA INITIO and ARISTADA<sup>11,14</sup>

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. 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.

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# CLINICAL PHARMACOLOGY FOR ARISTADA INITIO AND ARISTADA, (CONT.)

#### MEAN HALF-LIFE OF DAY-1 DOSING COMPONENTS 11,14



#### Elimination<sup>11,14</sup>

#### Metabolism of ARISTADA INITIO and ARISTADA

The biotransformation of ARISTADA INITIO and ARISTADA likely involves enzyme-mediated hydrolysis to form *N*-hydroxymethyl-aripiprazole, which subsequently undergoes hydrolysis to aripiprazole. Elimination of aripiprazole is mainly through hepatic metabolism involving CYP3A4 and CYP2D6.

#### **Excretion of ARISTADA INITIO**

For ARISTADA INITIO, the mean aripiprazole terminal elimination half-life was 15-18 days after injection. 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 INITIO administration.

#### **Excretion of ARISTADA**

The mean aripiprazole terminal elimination half-life ranged from 53.9 days to 57.2 days after monthly, every 6-week and every 2-month (1064 mg) injections of ARISTADA. 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 for ARISTADA INITIO and ARISTADA<sup>11,14</sup>

No specific drug interaction studies have been performed with ARISTADA INITIO or ARISTADA. The drug interaction data for ARISTADA INITIO and ARISTADA were obtained from studies with oral aripiprazole.

Based on a simulation, a 4.5-fold increase in mean  $C_{\rm max}$  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  $C_{\rm max}$  and AUC values at steady-state is expected in poor metabolizers of CYP2D6 administered with strong CYP3A4 inhibitors.





## INDICATION, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS FOR ARISTADA INITIO AND ARISTADA

#### Indication

ARISTADA INITIO® (aripiprazole lauroxil), in combination with oral aripiprazole, is indicated for the initiation of ARISTADA® (aripiprazole lauroxil) when used for the treatment of schizophrenia in adults.

ARISTADA is indicated for the treatment of schizophrenia in adults.

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 INITIO and ARISTADA are not approved for the treatment of patients with dementia-related psychosis.

#### Contraindication

Known hypersensitivity reaction to aripiprazole. Reactions have ranged from pruritus/urticaria to anaphylaxis.

#### Warnings and Precautions

Refer to the **Warnings and Precautions** section of the Prescribing Information for complete information.

#### **Increased Mortality in Elderly Patients with Dementia-related Psychosis**

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk 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 INITIO and ARISTADA are not approved for the treatment of patients with dementia-related psychosis.

#### **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 INITIO and ARISTADA are not approved for the treatment of patients with dementia-related psychosis.

#### **Potential for Dosing and Medication Errors**

Medication errors, including substitution and dispensing errors, between ARISTADA INITIO and ARISTADA could occur. ARISTADA INITIO is intended for single administration in contrast to ARISTADA which is administered monthly, every 6 weeks, or every 8 weeks. Do not substitute ARISTADA INITIO for ARISTADA because of differing pharmacokinetic profiles.

#### **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 INITIO and 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).





# INDICATION, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS FOR ARISTADA INITIO AND ARISTADA, (CONT.)

Warnings and Precautions, (CONT.)

#### **Neuroleptic Malignant Syndrome, (CONT.)**

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.

#### **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.

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

Given these considerations, antipsychotics 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, discontinuation should be considered. However, some patients may require antipsychotic treatment with ARISTADA despite the presence of the syndrome.

#### **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.





# INDICATION, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS FOR ARISTADA INITIO AND ARISTADA, (CONT.)

Warnings and Precautions, (CONT.)

Metabolic Changes, (CONT.)

#### 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.

#### Dyslipidemia

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

#### Weight Gain

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

#### **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. If compulsive urges develop, consider discontinuing aripiprazole.

#### **Orthostatic Hypotension**

Aripiprazole may cause orthostatic hypotension, perhaps due to its  $\alpha_l$ -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





# INDICATION, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS FOR ARISTADA INITIO AND ARISTADA, (CONT.)

#### Warnings and Precautions, (CONT.)

#### **Orthostatic Hypotension,** (CONT.)

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, monitor orthostatic vital signs.

#### **Falls**

Antipsychotics including ARISTADA INITIO® (aripiprazole lauroxil) and ARISTADA® (aripiprazole lauroxil) 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.

#### 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 antipsychotics 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 antipsychotics in patients with severe neutropenia (absolute neutrophil count <1000/mm³) and follow their WBC until recovery.

#### **Seizures**

As with other antipsychotic drugs, use ARISTADA INITIO and 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.

#### **Potential for Cognitive and Motor Impairment**

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

#### **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 INITIO and 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).

#### Dysphagia

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





# DOSING AND ADMINISTRATION FOR ARISTADA INITIO AND ARISTADA

Refer to the **Dosage and Administration** sections of the Prescribing Information for complete information.

#### Dosage and administration for ARISTADA INITIO<sup>11</sup>

ARISTADA INITIO® (aripiprazole lauroxil) is only to be used as a single dose to initiate ARISTADA® (aripiprazole lauroxil) treatment or as a single dose to re-initiate ARISTADA treatment following a missed dose of ARISTADA. ARISTADA INITIO is not for repeated dosing.

ARISTADA INITIO is not interchangeable with ARISTADA due to differing pharmacokinetic profiles.

ARISTADA INITIO is 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 INITIO. 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.

After establishing tolerability with oral aripiprazole, administer the first ARISTADA intramuscular injection (441 mg, 662 mg, 882 mg, or 1064 mg) in conjunction with both:

- One 675 mg injection of ARISTADA INITIO in the deltoid or gluteal muscle (which corresponds to 459 mg of aripiprazole); **and**
- One 30 mg dose of oral aripiprazole.

The first ARISTADA injection may be administered on the same day as ARISTADA INITIO or up to 10 days thereafter. Avoid injecting both ARISTADA INITIO and ARISTADA concomitantly into the same deltoid or gluteal muscle. ARISTADA INITIO is only available at a single strength as a single-dose pre-filled syringe, so dosage adjustments are not possible. Therefore, avoid use in patients who are known CYP2D6 poor metabolizers or taking strong CYP3A4 inhibitors, strong CYP2D6 inhibitors, strong CYP3A4 inducers, antihypertensive drugs or benzodiazepines.

#### Dosage and administration of ARISTADA14

ARISTADA can be initiated at a dose of 441 mg, 662 mg, 882 mg, administered monthly, or 1064 mg every 2 months.14

- Treatment may also be initiated with the 882-mg dose, administered every 6 weeks
- Administer ARISTADA either in the deltoid muscle (441-mg dose only) or gluteal muscle (441-mg, 662-mg, 882-mg, or 1064-mg doses)
- 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
- There are two ways to initiate treatment with ARISTADA:
  - Option #1: Administer one intramuscular injection of ARISTADA INITIO 675 mg (in either the deltoid or gluteal muscle) **and** one dose of oral aripiprazole 30 mg in conjunction with the first ARISTADA injection.
    - o The first ARISTADA injection may be administered on the same day as ARISTADA INITIO or up to 10 days thereafter. See the ARISTADA INITIO prescribing information for additional information regarding administration of ARISTADA INITIO.
    - o Avoid injecting both ARISTADA INITIO and ARISTADA concomitantly into the same deltoid or gluteal muscle.
  - Option #2: Administer 21 consecutive days of oral aripiprazole in conjunction with the first ARISTADA injection
- Dose of ARISTADA may be adjusted as needed. When making dose and dosing interval adjustments, the pharmacokinetics and prolonged-release characteristics of ARISTADA should be considered

Please see additional Important Safety Information on pages 38 to 39 and accompanying full Prescribing Information, including Boxed Warning, for <u>ARISTADA INITIO</u> and <u>ARISTADA</u>. ARISTADA INITIO® aripiprazole lauroxil extended-release injectable suspension ARISTADA aripiprazole lauroxil extended-release injectable suspension

441 mg 662 mg 882 mg 1064 mg

# DOSING AND ADMINISTRATION FOR ARISTADA INITIO AND ARISTADA, (CONT.)

 Missed Doses: If time elapsed since last injection exceeds 6 weeks (441 mg), 8 weeks (662 mg, 882 mg), or 10 weeks (1064 mg), supplement next ARISTADA injection with oral aripiprazole and/or ARISTADA INITIO as recommended in the full Prescribing Information for ARISTADA INITIO and ARISTADA

#### Official product labeling and literature

This is not all the information for the dosing and administration of ARISTADA INITIO and ARISTADA. Please see the full Prescribing Information for additional information.

#### Dosage forms, including strengths and package sizes<sup>11,14</sup>

ARISTADA INITIO® (aripiprazole lauroxil) is available in a strength of 675 mg in 2.4 mL. The kit contains a 5-mL pre-filled syringe containing ARISTADA INITIO as a sterile white to off-white aqueous suspension with safety needles.

Dosage Strength	Kit Configuration	National Drug Code (11 digit)
Arichael Con to	3 safety needles:	
ACTION AND THE STATE OF THE STA	<ul> <li>1-inch (25 mm) 21 gauge</li> <li>1½-inch (38 mm) 20 gauge</li> <li>2-inch (50 mm) 20 gauge</li> </ul>	65757-0500-03

ARISTADA® (aripiprazole lauroxil) extended-release injectable suspension is available in dosage strengths of 441 mg in 1.6 mL, 662 mg in 2.4 mL, 882 mg in 3.2 mL, and 1064 mg in 3.9 mL. Each kit contains a 5-mL single dose, pre-filled syringe containing ARISTADA sterile aqueous suspension and safety needles.

Dosage Strength	Kit Configuration	National Drug Code (11 digit)
Anthoris 441   19   19   19   19   19   19   19	3 safety needles:  • 1-inch (25 mm) 21 gauge  • 1½-inch (38 mm) 20 gauge  • 2-inch (50 mm) 20 gauge	65757-0401-03
Artistady  Artistady  The far annual man of the control of the con	2 safety needles: • 1½-inch (38 mm) 20 gauge • 2-inch (50 mm) 20 gauge	65757-0402-03
Artifacts  William Internation  The Part Artifacts  The Part Artif	2 safety needles: • 1½-inch (38 mm) 20 gauge • 2-inch (50 mm) 20 gauge	65757-0403-03
A Comment of the Comm	2 safety needles: • 1½-inch (38 mm) 20 gauge • 2-inch (50 mm) 20 gauge	65757-0404-03

Please see additional Important Safety Information on pages 38 to 39 and accompanying full Prescribing Information, including Boxed Warning, for <u>ARISTADA INITIO</u> and <u>ARISTADA</u>. ARISTADA
INITIO®
aripiprazole lauroxil
extended-release injectable suspension

ARISTADA aripiprazole lauroxil extended-release injectable suspension

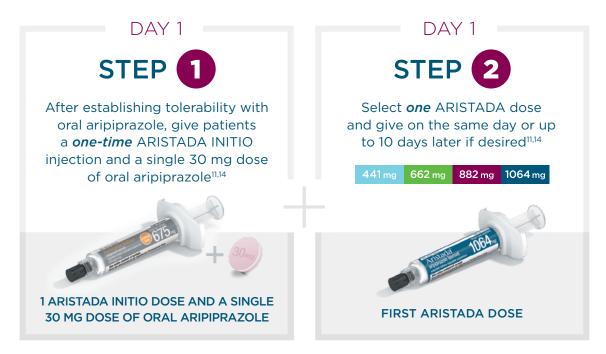
441 mg 662 mg 882 mg 1064 mg

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# DOSING AND ADMINISTRATION FOR ARISTADA INITIO AND ARISTADA, (CONT.)

#### To initiate treatment with ARISTADA INITIO<sup>11,14</sup>:

 Administer 1 injection of 675 mg of ARISTADA INITIO® (aripiprazole lauroxil) and 1 dose of oral aripiprazole 30 mg in conjunction with the first ARISTADA® (aripiprazole lauroxil) injection (441 mg, 662 mg, 882 mg, or 1064 mg). The first ARISTADA injection may be administered on the same day as ARISTADA INITIO or up to 10 days thereafter



#### Storage for ARISTADA INITIO<sup>11</sup>

ARISTADA INITIO should be stored 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). **Do not freeze.**<sup>11</sup>

- Store each product properly per instructions on carton(s)<sup>11</sup>
- ARISTADA INITIO cartons should lay flat when stored and should not be shelved vertically. The carton is shaped to assist with proper storage. Proper storage of ARISTADA INITIO should prevent excessive sediment near needle hub<sup>19</sup>
- The storage shelf life for ARISTADA INITIO is 24 months from date of manufacture<sup>19</sup>

#### Storage for ARISTADA<sup>14</sup>

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).

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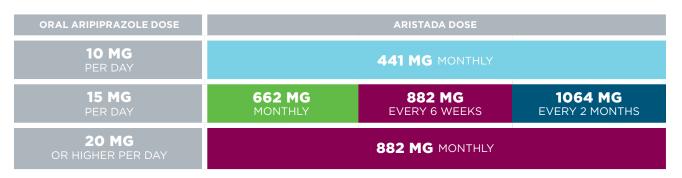


# DOSING AND ADMINISTRATION FOR ARISTADA INITIO AND ARISTADA, (CONT.)

Recommended ARISTADA doses based on oral aripiprazole total daily dose<sup>11,14</sup>

For patients who are stabilized on oral aripiprazole, the ARISTADA® (aripiprazole lauroxil) doses for patients are as follows:

#### TRANSITIONING PATIENTS ON ORAL ARIPIPRAZOLE TO ARISTADA<sup>14</sup>



In conjunction with the first ARISTADA injection, administer 1 injection of ARISTADA INITIO® (aripiprazole lauroxil) and one 30 mg dose of oral aripiprazole or continue treatment with oral aripiprazole for 21 consecutive days.<sup>11,14</sup>

Dose may be adjusted as needed. When making dose and dosing interval adjustments, the pharmacokinetics and prolonged-release characteristics of ARISTADA should be considered.<sup>14</sup>

#### Early dosing<sup>14</sup>

The recommended ARISTADA dosing interval of 441 mg, 662 mg, and 882 mg monthly; 882 mg every 6 weeks; or 1064 mg every 2 months should be maintained. In the event of early dosing, an ARISTADA injection should not be given earlier than 14 days after the previous injection.





# MISSED DOSE RECOMMENDATION FOR ARISTADA

#### Missed dose recommendation<sup>11,14</sup>

ARISTADA INITIO® (aripiprazole lauroxil) may be used to re-initiate treatment with ARISTADA® (aripiprazole lauroxil) following a missed dose of ARISTADA. When a dose of ARISTADA is missed, administer the next injection of ARISTADA as soon as possible. The need to restart oral aripiprazole, ARISTADA INITIO, or ARISTADA INITIO and a 30 mg dose of oral aripiprazole after a missed dose of ARISTADA depends upon the dose and the time since the last injection. Depending on the time elapsed since the last ARISTADA injection, supplement the next ARISTADA injection as recommended in the table below.

#### REINITIATING ARISTADA TREATMENT AFTER MISSING A DOSE14

	LENGTH OF TIME SINCE LAST INJECTION			
DOSE OF LAST ARISTADA INJECTION	No supplementation required	Supplement with a single dose of ARISTADA INITIO <b>OR</b> 7 days of oral aripiprazole <sup>a</sup>	Reinitiate with a single dose of ARISTADA INITIO and a single dose of 30 mg oral aripiprazole <b>OR</b> supplement with 21 days of oral aripiprazole <sup>a</sup>	
<b>1064 MG</b> EVERY 2 MONTHS	≤10 weeks	>10 and ≤12 weeks	>12 weeks	
<b>882 MG</b> MONTHLY & EVERY 6 WEEKS	≤8 weeks	>8 and ≤12 weeks	>12 weeks	
662 MG MONTHLY	≤8 weeks	>8 and ≤12 weeks	>12 weeks	
441 MG MONTHLY	≤6 weeks	>6 and ≤7 weeks	>7 weeks	

<sup>&</sup>lt;sup>a</sup>The patient should supplement with the same dose of oral aripiprazole as when the patient began ARISTADA.<sup>14</sup>

Please see additional Important Safety Information on pages 38 to 39 and accompanying full Prescribing Information, including Boxed Warning, for ARISTADA INITIO and ARISTADA.

ARISTADA INITIO® aripiprazole lauroxil extended-release injectable suspension

ARISTADA® aripiprazole lauroxil extended-release injectable suspension

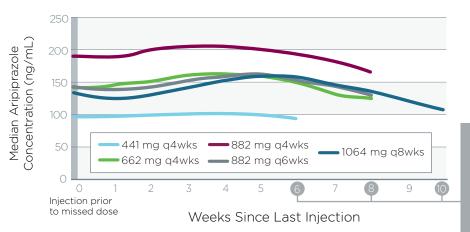
441 mg 662 mg 882 mg 1064 mg

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## MISSED DOSE RECOMMENDATION FOR ARISTADA, (CONT.)

MODELED PLASMA CONCENTRATIONS FOLLOWING A SINGLE DOSE AT STEADY STATE<sup>19\*†</sup>



- \* Median aripiprazole concentrations simulated following the last ARISTADA injection at steady-state.
- † Steady-state is achieved 4 months following treatment initiation.

ARISTADA® (aripiprazole lauroxil) dosing intervals: The 441-mg and 662-mg doses are given monthly; the 882-mg dose is given monthly or every 6 weeks; and the 1064-mg dose is given every 2 months<sup>14</sup>





# DOSAGE ADJUSTMENTS FOR CYP450 CONSIDERATIONS

#### ARISTADA INITIO dosage adjustment for CYP450 considerations<sup>11</sup>

ARISTADA INITIO® (aripiprazole lauroxil) is only available at a single strength as a single dose pre-filled syringe, so dosage adjustments are not possible. Avoid use in patients who are known CYP2D6 poor metabolizers or taking strong CYP3A4 inhibitors, strong CYP2D6 inhibitors, or strong CYP3A4 inducers, antihypertensive drugs or benzodiazepines.

#### ARISTADA dosage adjustment for CYP450 considerations<sup>14</sup>

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® (aripiprazole lauroxil). Avoid initiating ARISTADA treatment with ARISTADA INITIO in patients requiring dose adjustments.

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

- No dosage changes are recommended for ARISTADA, if CYP450 modulators are added for less than 2 weeks
- Make the following dose changes to ARISTADA if CYP450 modulators are added for greater than 2 weeks

#### ARISTADA DOSE ADJUSTMENTS WITH CONCOMITANT CYP450 MODULATOR USE<sup>14</sup>

Concomitant Medicine	Dose Change for ARISTADA
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, 882 mg, or 1064 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, 882 mg or 1064 mg dose. No dosage adjustment is necessary in patients taking 441 mg ARISTADA, if tolerated.
CYP3A4 Inducers	No dose adjustment for 662 mg, 882 mg or 1064 mg dose; increase the 441 mg dose to 662 mg.

<sup>\*</sup> For the 882 mg dose administered every 6 weeks and the 1064 mg dose administered every 2 months, the next lower strength should be 441 mg administered monthly.

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## DOSAGE MODIFICATIONS IN SPECIAL POPULATIONS

#### ARISTADA INITIO and ARISTADA dosage modifications in special populations<sup>11,14</sup>

No dosage adjustment for ARISTADA INITIO® (aripiprazole lauroxil) or ARISTADA® (aripiprazole lauroxil) are required on the basis of a patient's sex, race, or smoking status.

No dosage adjustment for ARISTADA INITIO or ARISTADA are 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/min).

ARISTADA dosage adjustment is recommended in known CYP2D6 poor metabolizers due to high aripiprazole concentrations.

Avoid use of ARISTADA INITIO in these patients because dosage adjustments are not possible (it is only available in 1 strength in a single dose pre-filled syringe).

Refer to the **Pediatric Use** and **Geriatric Use** sections on page 29 for information on use in pediatric and geriatric patient populations.





# DRUG INTERACTIONS FOR ARISTADA INITIO

#### Drugs having clinically important interactions with ARISTADA INITIO<sup>11</sup>

Concomitant drugs or drug classes that interact with ARISTADA INITIO® (aripiprazole lauroxil) are shown below. Refer to the **Drug Interactions** section of the Prescribing Information for complete information.

#### CLINICALLY IMPORTANT DRUG INTERACTIONS WITH ARISTADA INITIO<sup>11</sup>

	Strong CYP3A4 Inhibitors and CYP2D6 Inhibitors	
Clinical Impact:	Concomitant use of oral aripiprazole with strong CYP3A4 or CYP2D6 inhibitors increased the exposure of aripiprazole compared to the use of oral aripiprazole alone.	
Intervention:	Avoid concomitant use of ARISTADA INITIO with strong CYP3A4 or strong CYP2D6 inhibitors because the dosage of ARISTADA INITIO cannot be modified.	
Examples:	itraconazole, clarithromycin, quinidine, fluoxetine, paroxetine	
	Strong CYP3A4 Inducers	
Clinical Impact:	Concomitant use of oral aripiprazole and carbamazepine decreased the exposure of aripiprazole compared to the use of oral aripiprazole alone.	
Intervention:	Avoid concomitant use of ARISTADA INITIO with strong CYP3A4 inducers because the dosage of ARISTADA INITIO cannot be modified.	
Examples:	carbamazepine, rifampin	
Antihypertensive Drugs		
Clinical Impact:	Due to its alpha adrenergic antagonism, aripiprazole has the potential to enhance the effec of certain antihypertensive agents.	
Intervention:	Avoid concomitant use of ARISTADA INITIO with antihypertensive drugs because the	
	dosage of ARISTADA INITIO cannot be modified.	
Examples:	carvedilol, lisinopril, prazosin	
Examples:	-	
Examples:  Clinical Impact:	carvedilol, lisinopril, prazosin	
	carvedilol, lisinopril, prazosin  Benzodiazepines  The intensity of sedation was greater with the combination of oral aripiprazole and lorazep as compared to that observed with aripiprazole alone. The orthostatic hypotension observed	





## DRUG INTERACTIONS FOR ARISTADA

#### Drugs having clinically important interactions with ARISTADA<sup>14</sup>

Concomitant drugs or drug classes that interact with and ARISTADA® (aripiprazole lauroxil) are shown below. Refer to the **Drug Interactions** section of the Prescribing Information for complete information.

#### CLINICALLY IMPORTANT DRUG INTERACTIONS WITH ARISTADA<sup>14</sup>

	Strong CYP3A4 Inhibitors and CYP2D6 Inhibitors
Clinical Impact:	The concomitant use of oral aripiprazole with strong CYP3A4 or CYP2D6 inhibitors increase the exposure of aripiprazole compared to the use of oral aripiprazole alone.
Intervention:	With concomitant use of ARISTADA with a strong CYP3A4 inhibitor or CYP2D6 inhibitor for more than 2 weeks, reduce the ARISTADA dose.
Examples:	itraconazole, clarithromycin, quinidine, fluoxetine, paroxetine
_	Strong CYP3A4 Inducers
Clinical Impact:	The concomitant use of oral aripiprazole and carbamazepine decreased the exposure of aripiprazole compared to the use of oral aripiprazole alone.
Intervention:	With concomitant use of ARISTADA with a strong CYP3A4 inducer for more than 2 weeks consider increasing the ARISTADA dose.
Examples:	carbamazepine, rifampin
Antihypertensive Drugs	
Clinical Impact:	Due to its alpha adrenergic antagonism, aripiprazole has the potential to enhance the effect certain antihypertensive agents.
Intervention:	Monitor blood pressure and adjust dose accordingly.
Examples:	carvedilol, lisinopril, prazosin
	Benzodiazepines
Clinical Impact:	The intensity of sedation was greater with the combination of oral aripiprazole and lorazepa 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.
Intervention:	Monitor sedation and blood pressure. Adjust dose accordingly.
Examples:	lorazepam





# ADVERSE REACTIONS AND SAFETY DATA FOR ARISTADA INITIO AND ARISTADA

#### Safety of ARISTADA INITIO

- In pharmacokinetic studies, the safety profile of ARISTADA INITIO® (aripiprazole lauroxil) was generally consistent with that observed for ARISTADA® (aripiprazole lauroxil)<sup>11</sup>
- The most commonly observed adverse reaction was akathisia in the 12-week clinical trial for ARISTADA<sup>11,14</sup>
- A phase 1 study evaluating the safety, tolerability, and pharmacokinetics of the two initiation regimens was conducted (N = 161). In this study, patients received 21 days of oral aripiprazole (15 mg daily dose) and 1 ARISTADA dose (n = 81) or 1 injection of ARISTADA INITIO plus a single dose of 30 mg oral aripiprazole and 1 ARISTADA dose (n = 80). Patients were randomized 1:1:1:1 to receive an ARISTADA dose of either 441 mg or 882 mg<sup>21</sup>
  - There were 2 cases of akathisia in the 21-day oral aripiprazole arms (2 mild cases)
  - There were 4 cases of akathisia in the ARISTADA INITIO arms (3 mild cases, 1 moderate case)
  - None of the patients experienced serious adverse events or discontinued participation in the trial due to akathisia
- In pharmacokinetic studies evaluating ARISTADA INITIO, the incidences of injection-site reactions with ARISTADA INITIO were similar to the incidence observed for ARISTADA<sup>11</sup>

Refer to the **Adverse Reactions** section of the ARISTADA Prescribing Information for randomized, placebo-controlled Phase 3 clinical study experience of aripiprazole lauroxil in the schizophrenia patient population.

#### ARISTADA INITIO and ARISTADA patient exposure<sup>11,14</sup>

In clinical trials in adult patients with schizophrenia, ARISTADA INITIO has been evaluated for safety in 170 patients and ARISTADA has been evaluated for safety in 1,180 patients.

#### Commonly observed adverse reactions with ARISTADA<sup>14</sup>

In the 12-week placebo-controlled, fixed-dose schizophrenia trial (441 mg monthly and 882 mg monthly), the most common adverse reaction (incidence ≥5% and at least twice the rate of placebo reported by patients treated with ARISTADA 441 mg and 882 mg monthly) was akathisia.

ADVERSE REACTIONS IN ≥2% OF ARISTADA-TREATED PATIENTS AND THAT OCCURRED AT GREATER INCIDENCE THAN IN PLACEBO-TREATED PATIENTS IN THE 12-WEEK CLINICAL TRIAL<sup>14</sup>

Adverse reactions	Placebo N = 207	ARISTADA 441 mg monthly N = 207	ARISTADA 882 m monthly N = 208
Injection-site pain	2%	3%	4%
Increased weight	1%	2%	2%
Increased blood creatine phosphokinase	0%	2%	1%
Akathisia	4%	11%	11%
Headache	3%	3%	5%
Insomnia	2%	3%	4%
Restlessness	1%	3%	1%

In an open-label pharmacokinetic study, the adverse reactions associated with the use of ARISTADA were similar across the 441 mg monthly, 882 mg every 6 weeks, and 1064 mg every 2 months dose groups.<sup>14</sup>





# ARISTADA INITIO AND ARISTADA USE IN SPECIFIC POPULATIONS

Refer to the **Use in Specific Populations** section of the Prescribing Information for complete information.

#### Pregnancy exposure registry<sup>11,14</sup>

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ARISTADA INITIO® (aripiprazole lauroxil) and/or ARISTADA® (aripiprazole lauroxil) during pregnancy. For more information, contact the National Pregnancy Registry for Atypical Antipsychotics at 1-866-961-2388 or visit <a href="http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/">http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/</a>.

#### Pregnancy risk summarv<sup>11,14</sup>

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 8 and 23 times, respectively, the maximum recommended human dose (MRHD) of 675 mg based on body surface area (mg/m²). However, aripiprazole caused developmental toxicity and possible teratogenic effects in rats and rabbits. 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.

#### Lactation risk summary<sup>11,14</sup>

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 INITIO and/or ARISTADA and any potential adverse effects on the breastfed infant from ARISTADA INITIO and/or ARISTADA from the underlying maternal condition.

#### Pediatric use<sup>11,14</sup>

Safety and effectiveness of ARISTADA INITIO and/or ARISTADA in pediatric patients (<18 years of age) have not been established.

#### Geriatric use<sup>11,14</sup>

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

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. ARISTADA INITIO and ARISTADA are not approved for the treatment of patients with dementia-related psychosis.

#### CYP2D6 poor metabolizers<sup>11,14</sup>

Approximately 8% of Caucasians and 3-8% of Black/African Americans cannot metabolize CYP2D6 substrates and are classified as poor metabolizers (PM). Avoid use of ARISTADA INITIO in these patients because dosage adjustments are not possible (it is only available in 1 strength in a single dose pre-filled syringe). ARISTADA dosage adjustment is recommended in known CYP2D6 poor metabolizers due to high aripiprazole concentrations.

#### Hepatic and renal impairment<sup>11,14</sup>

No dosage adjustment for ARISTADA INITIO or 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).





## ARISTADA CLINICAL STUDIES

#### Efficacy of ARISTADA (441 mg monthly and 882 mg monthly)<sup>14</sup>

Efficacy of ARISTADA® (aripiprazole lauroxil) (441 mg monthly and 882 mg monthly) 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 monthly], 208 [ARISTADA 882 mg monthly], 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 the Positive and Negative Syndrome Scale (PANSS) and the 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). PANSS total 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  $\ge$ 4 for at least 2 of the selected Positive Scale items. Patients were also required to have a CGI-S Score of  $\ge$ 4.

#### Primary efficacy endpoint<sup>14</sup>

The primary efficacy variable was the change from baseline to endpoint (Day 85) in the Positive and Negative Syndrome Scale (PANSS) total score. Statistically significant separation from placebo on PANSS total score change was observed in each ARISTADA dose group as identified in the table on the following page.

#### PRIMARY EFFICACY RESULTS<sup>14</sup>

Study	Treatment	Primary Efficacy Measure: PANSS Total Score			
Number	Group	Mean Baseline Score (SD)	LS Mean Change From Baseline (SE)	Placebo-subtracted Difference* (95% CI)	
	ARISTADA 441 mg <sup>+</sup> monthly	92.6 (10.2)	-20.9 (1.4)	-10.9 (-14.5, -7.3)	
Study 1	ARISTADA 882 mg† monthly	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.

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

<sup>†</sup> Doses that are demonstrated to be effective.

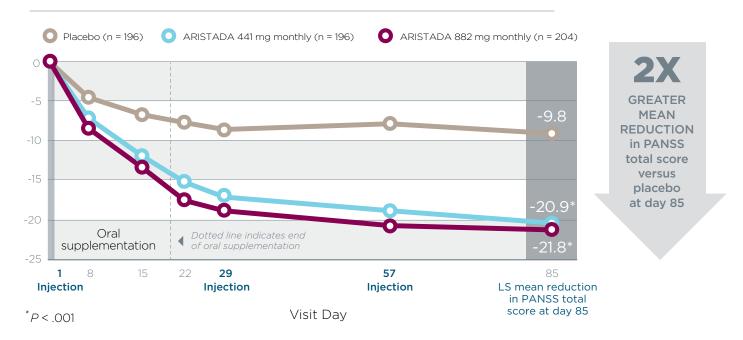
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PANSS total score change for each treatment group (441 mg, 882 mg) is shown in the chart below.

# CHANGE FROM PANSS TOTAL SCORE: BASELINE AT DAY 85 (PRIMARY ENDPOINT)<sup>14,20</sup>



Abbreviations: LS, least squares; PANSS, Positive and Negative Syndrome Scale.

- Patients enrolled in the 12-week clinical trial were considered markedly ill, with mean baseline Positive and Negative Syndrome Scale (PANSS) total scores of 93.9 (placebo), 92.6 (ARISTADA 441 mg monthly), and 92.0 (ARISTADA 882 mg monthly)<sup>13,22</sup>
- In a post hoc analysis† of the 12-week phase 3 clinical trial, improvement was seen in a subgroup of patients with more severe symptoms. Patients with PANSS total score >92 at baseline showed a mean reduction in PANSS total score from baseline to day 85. Those receiving placebo (n = 99), ARISTADA 441 mg monthly (n = 95), and ARISTADA 882 mg monthly (n = 100) experienced a mean decrease in PANSS total scores of 7.44, 22.14, and 24.05, respectively<sup>23</sup>
- <sup>†</sup> Post hoc analysis: The 12-week phase 3 study was not designed to prospectively assess, nor was it adequately powered to examine, the efficacy of ARISTADA in the treatment of this subgroup of patients. Therefore, there are limitations to these data, and no conclusions can be drawn from this post hoc analysis.

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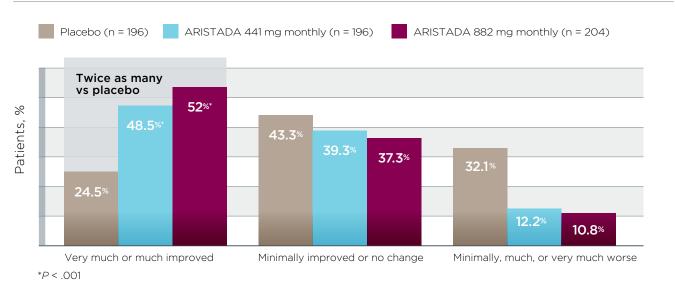


#### Secondary efficacy endpoint<sup>19,20</sup>

The secondary efficacy endpoint was defined as the CGI-I score at Day 85. Both ARISTADA® (aripiprazole lauroxil) treatment groups demonstrated statistically significantly better CGI-I scores vs placebo.

The CGI-I Scale scale allows the clinician to assess and rate improvement in mental illness on a scale of 1 (very much improved) to 7 (very much worse) based on the change in clinical condition from baseline. For the secondary endpoint, approximately 50% of patients receiving ARISTADA had CGI-I scores that were "very much improved" or "much improved" at Day 85. Twice as many patients were "very much improved" or "much improved" in the ARISTADA arm vs those in the placebo arm.

#### CGI-I SCORE AT DAY 85 (SECONDARY ENDPOINT)19



Abbreviation: CGI-I, Clinical Global Impression-Improvement.

- In an exploratory analysis, improvement in CGI-I was seen for both ARISTADA groups vs the placebo group at each post-baseline visit<sup>20</sup>
- <sup>†</sup> Exploratory analysis: Analysis of all exploratory endpoints was supportive of the prespecified key primary and secondary endpoints. However, these analyses do not allow definitive efficacy conclusions regarding treatment effects of ARISTADA to be drawn.

#### Efficacy of other doses

- The efficacy of ARISTADA 662 mg every month, 882 mg every 6 weeks, and 1064 mg every 2 months in the treatment of adults with schizophrenia was established by pharmacokinetic bridging studies
- These dosing regimens resulted in plasma aripiprazole concentrations that are within the range established by doses of 441 mg monthly and 882 mg monthly

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ARISTADA 52-WEEK SAFETY STUDY: EXPLORING SAFETY AND THERAPEUTIC EFFECT OF ARISTADA IN CONTINUING AND DE NOVO PATIENTS<sup>25</sup>

#### STUDY DESIGN<sup>25</sup>

- This was a 52-week open-label safety study of 2 fixed doses of ARISTADA® (aripiprazole lauroxil) 441 mg or 882 mg administered by intramuscular injection every 4 weeks
- The study enrolled 236 patients who completed the 12-week phase 3 study, as well as 242 new adults with chronic stable schizophrenia, all of which were administered 882 mg of ARISTADA by intramuscular injection every 4 weeks
- Patients on prior placebo and de novo patients received active oral aripiprazole 21-day supplementation, whereas patients who had received prior active ARISTADA received placebo

#### STUDY OUTCOMES<sup>25</sup>

 The primary objective was to assess the long-term safety and tolerability of ARISTADA in patients with stable schizophrenia

#### ADVERSE EVENTS (AES) OCCURRING IN ≥2% OF PATIENTS DURING THE 52-WEEK STUDY<sup>25</sup>

	ADICTADA 441	A DISTADA 200 mm	
AE	ARISTADA 441 mg monthly (N = 110)	ARISTADA 882 mg monthly (N = 368)	Both ARISTADA doses (N = 478)
Any AE	46%	52%	50%
Insomnia	3%	10%	8%
Weight increased	6%	5%	5%
Anxiety	4%	5%	4%
Injection-site pain	1%	5%ª	4%
Akathisia	1%	5%	4%
Headache	6%	3%	4%
Schizophrenia	4%	3%	3%
Nasopharyngitis	4%	3%	3%
Weight decreased	3%	2%	3%
Tremor	1%	3%	3%

- Adverse events leading to discontinuation were reported in 5.9% (n = 28) of the total population (N=478)<sup>25</sup>
- Adverse events were generally consistent with what is established and known of the safety of aripiprazole<sup>25</sup>
- No new safety events were observed during this 52-week safety study<sup>25</sup>
- <sup>a</sup> Majority reported in de novo patients (16 patients)<sup>25</sup>

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Please see additional Important Safety Information on pages 38 to 39 and accompanying full Prescribing Information, including Boxed Warning, for ARISTADA INITIO and ARISTADA.

**ARISTADA** aripiprazole lauroxil extended-release injectable suspension

aripiprazole lauroxil extended-release injectable suspension 441 mg 662 mg 882 mg 1064 mg

#### Long-term safety study, (CONT.)

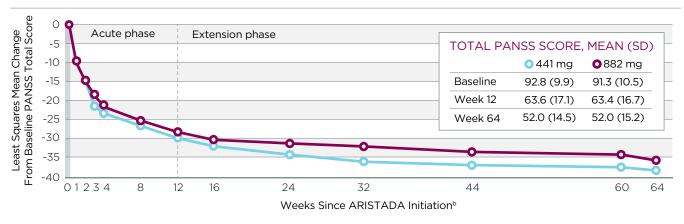
The durability of effect of ARISTADA was observed over the 52-week safety study period (secondary outcome)

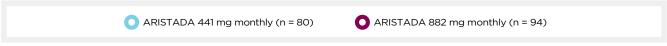
• The results of the study demonstrate the safety and tolerability of the long-term treatment with aripiprazole lauroxil in patients with schizophrenia<sup>25</sup>

#### Long-term efficacy was further evaluated in a post hoc analysis<sup>24</sup>

- A post hoc analysis assessed long-term outcomes for a subgroup of patients (N = 174) who entered a 52-week safety study after being successfully stabilized during a pivotal 12-week, placebo-controlled, randomized clinical trial and had at least 1 Positive and Negative Syndrome Scale (PANSS) assessment after drug administration in the safety study $^{20,24*}$
- Patients received 1 of 2 doses of ARISTADA (441 mg or 882 mg) administered by intramuscular injection every 4 weeks during both the 12-week study and the extension study<sup>24</sup>
- The objective was to evaluate the durability of the therapeutic effect of long-term treatment with ARISTADA in patients with schizophrenia following successful treatment of an acute psychotic episode<sup>24</sup>
- Patients from the acute-phase study who continued in the 52-week study were observed to have sustained and gradual improvements in PANSS total score for both dose groups through week 64 (least squares mean [standard error] change from week 12 was -8.1 [1.3] and -7.2 [1.2] for the 441 mg and 882 mg cohorts, respectively)<sup>24\*</sup>

# MEAN CHANGE FROM BASELINE IN PANSS TOTAL SCORE IN ACTIVE ROLLOVER PATIENT SUBGROUP<sup>24, a</sup>





<sup>a</sup>In patients who had at least 1 PANSS assessment after drug administration in the 52-week safety study.<sup>14</sup> <sup>b</sup>Indicated weeks denote assessment time points.<sup>14</sup>

\*This post hoc analysis of active rollover patients from the 12-week acute-phase study was not designed to prospectively assess, nor was it powered to examine, the efficacy of ARISTADA in this subgroup of patients. No definitive conclusions of efficacy can be drawn from these results.

In addition to the inherent limitations of post hoc analyses, limitations of this analysis include the preferential selection of study participants and differing assessment intervals between the 12-week study and the 52-week safety study.<sup>24</sup>

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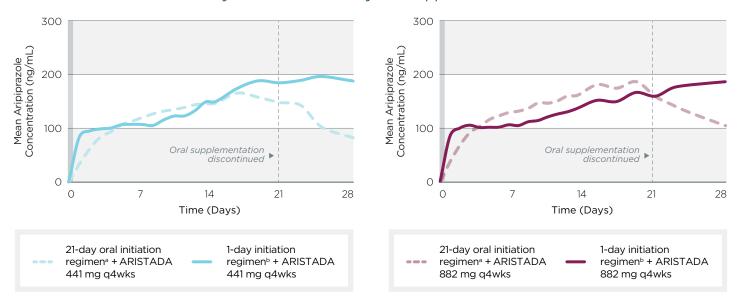
Abbreviation: SD, standard deviation.

The effectiveness of ARISTADA® (aripiprazole lauroxil) when treatment is initiated with 21 days of oral aripiprazole was established based on randomized, placebo-controlled, Phase 3 clinical studies in patients with schizophrenia.

ARISTADA treatment initiation with 1 injection of ARISTADA INITIO® (aripiprazole lauroxil) plus a 30 mg dose of oral aripiprazole in the treatment of adults with schizophrenia was established by a pharmacokinetic bridging study which demonstrated that this initiation regimen resulted in plasma aripiprazole concentrations that are comparable to those achieved when ARISTADA treatment is initiated with 21 days of oral aripiprazole.<sup>14,19</sup>

#### OBSERVED MEAN ARIPIPRAZOLE CONCENTRATIONS OVER TIME<sup>26</sup>

#### Day 1 initiation vs 21-day oral supplementation



Results from a phase 1 study of initiation regimens for the ARISTADA doses of 441 mg or 882 mg with oral aripiprazole for 21 days compared to initiation regimens for ARISTADA doses of 441 mg or 882 mg with ARISTADA INITIO (675 mg) and a single 30 mg dose of oral aripiprazole.<sup>26</sup>





<sup>&</sup>lt;sup>a</sup>21-day oral initiation regimen consisted of 15 mg of oral aripiprazole for 21 days.<sup>26</sup>

<sup>&</sup>lt;sup>61</sup>-day initiation regimen consisted of a single ARISTADA INITIO injection (675 mg) and a single 30 mg dose of oral aripiprazole.<sup>26</sup>

# ARISTADA INITIO AND ARISTADA PATIENT COUNSELING INFORMATION

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

#### 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.

#### 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.

#### 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.

#### 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.

#### 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, or re-initiating treatment.

#### 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.

#### Leukopenia, Neutropenia and Agranulocytosis

Advise patients with a pre-existing low WBC count or a history of drug-induced leucopenia/neutropenia that they should have their CBC monitored.

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## ARISTADA INITIO AND ARISTADA PATIENT COUNSELING INFORMATION, (CONT.)

#### Interference with Cognitive and Motor Performance

Because ARISTADA INITIO® (aripiprazole lauroxil) and ARISTADA® (aripiprazole lauroxil) 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 therapy does not affect them adversely.

#### Heat Exposure and Dehydration

Advise patients regarding appropriate care in avoiding overheating and dehydration.

#### Concomitant Medication

Advise patients to inform their physicians if they are taking, or plan to take, any prescription or over-thecounter drugs, since there is a potential for interactions.

#### Pregnancy

Advise patients that ARISTADA INITIO and ARISTADA may cause extrapyramidal and/or withdrawal symptoms in a neonate and to notify their healthcare provider with a known or suspected pregnancy.

#### Pregnancy Registry

Advise patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ARISTADA INITIO and ARISTADA during pregnancy.





## IMPORTANT SAFETY INFORMATION FOR ARISTADA INITIO AND ARISTADA

**INDICATION and IMPORTANT SAFETY INFORMATION for ARISTADA INITIO®** (aripiprazole lauroxil) and ARISTADA® (aripiprazole lauroxil) extended-release injectable suspension, for intramuscular use

#### **INDICATION**

ARISTADA INITIO, in combination with oral aripiprazole, is indicated for the initiation of ARISTADA when used for the treatment of schizophrenia in adults.

ARISTADA is indicated for the treatment of schizophrenia in adults.

#### IMPORTANT SAFETY 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 INITIO and ARISTADA are not approved for the treatment of patients with dementia-related psychosis.

Contraindication: Known hypersensitivity reaction to aripiprazole. Reactions have ranged from pruritus/urticaria to anaphylaxis.

#### **Cerebrovascular Adverse Reactions, Including Stroke:**

Increased incidence of cerebrovascular adverse reactions (e.g., stroke, transient ischemic attack), including fatalities. have been reported in placebo-controlled trials of elderly patients with dementia-related psychosis treated with risperidone, aripiprazole, and olanzapine. ARISTADA INITIO and ARISTADA are not approved for the treatment of patients with dementia-related psychosis.

#### Potential for Dosing and Medication Errors:

Medication errors, including substitution and dispensing errors, between ARISTADA INITIO and ARISTADA could occur. ARISTADA INITIO is intended for single administration in contrast to ARISTADA which is administered monthly, every 6 weeks, or every 8 weeks. Do not substitute ARISTADA INITIO for ARISTADA because of differing pharmacokinetic profiles.

Neuroleptic Malignant Syndrome (NMS): A potentially fatal symptom complex may occur with administration of antipsychotic drugs, including ARISTADA INITIO and ARISTADA. Clinical manifestations of NMS include hyperpyrexia, muscle rigidity, altered mental status, and

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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 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.

Tardive Dyskinesia (TD): The risk of developing TD (a syndrome of abnormal, involuntary movements) and the potential for it to become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic increase. The syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. Prescribing antipsychotics should be consistent with the need to minimize TD. Discontinue ARISTADA if clinically appropriate. TD may remit, partially or completely, if antipsychotic treatment is withdrawn.

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

#### Hyperglycemia/Diabetes Mellitus:

Hyperglycemia, in some cases extreme and associated with ketoacidosis, coma, or death, has been reported in patients treated with atypical antipsychotics. There have been reports of hyperglycemia in patients treated with oral aripiprazole. Patients with diabetes should be regularly monitored for worsening of glucose control; those with risk factors for diabetes should undergo baseline and periodic fasting blood glucose testing. 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 should also undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients require continuation of antidiabetic treatment despite discontinuation of the suspect drug.

- **Dyslipidemia:** Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.
- Weight Gain: Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

#### **Pathological Gambling and Other Compulsive Behaviors:**

Compulsive or uncontrollable urges to gamble have been reported with use of aripiprazole. Other compulsive urges less frequently reported include sexual urges, shopping, binge eating and other impulsive or compulsive behaviors which may result in harm for the patient and others if not recognized. Closely monitor patients and consider dose reduction or stopping aripiprazole if a patient develops such urges.

# **ARISTADA**

aripiprazole lauroxil extended-release injectable suspension



441 mg 662 mg 882 mg 1064 mg

## IMPORTANT SAFETY INFORMATION FOR ARISTADA INITIO AND ARISTADA, (CONT.)

Orthostatic Hypotension: Aripiprazole may cause orthostatic hypotension which can be associated with dizziness, lightheadedness, and tachycardia. Monitor heart rate and blood pressure, and warn patients with known cardiovascular or cerebrovascular disease and risk of dehydration and syncope.

Falls: Antipsychotics including ARISTADA INITIO® (aripiprazole lauroxil) and ARISTADA® (aripiprazole lauroxil) may cause somnolence, postural hypotension or motor and sensory instability which may lead to falls and subsequent injury. Upon initiating treatment and recurrently, complete fall risk assessments as appropriate.

#### Leukopenia, Neutropenia, and Agranulocytosis:

Leukopenia, neutropenia and agranulocytosis have been reported with antipsychotics. Monitor complete blood count in patients with pre-existing low white blood cell count (WBC)/absolute neutrophil count or history of drug-induced leukopenia/neutropenia. Discontinue ARISTADA INITIO and/or ARISTADA at the first sign of a clinically significant decline in WBC and in severely neutropenic patients.

Seizures: Use with caution in patients with a history of seizures or with conditions that lower the seizure threshold.

#### **Potential for Cognitive and Motor Impairment:**

ARISTADA INITIO and ARISTADA may impair judgment, thinking, or motor skills. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are certain therapy with ARISTADA INITIO and/or ARISTADA does not affect them adversely.

Body Temperature Regulation: Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Advise patients regarding appropriate care in avoiding overheating and dehydration. Appropriate care is advised for patients who may exercise strenuously, may be exposed to extreme heat, receive concomitant medication with anticholinergic activity, or are subject to dehydration.

Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use; use caution in patients at risk for aspiration pneumonia.

Concomitant Medication: ARISTADA INITIO is only available at a single strength as a single-dose pre-filled syringe, so dosage adjustments are not possible. Avoid use in patients who are known CYP2D6 poor metabolizers or taking strong CYP3A4 inhibitors, strong CYP2D6 inhibitors, or strong CYP3A4 inducers, antihypertensive drugs or benzodiazepines.

Depending on the ARISTADA dose, adjustments may be recommended if patients are 1) known as CYP2D6 poor metabolizers and/or 2) taking strong CYP3A4 inhibitors, strong CYP2D6 inhibitors, or strong CYP3A4 inducers for greater than 2 weeks. Avoid use of ARISTADA 662 mg, 882 mg, or 1064 mg for patients taking both strong CYP3A4 inhibitors and strong CYP2D6 inhibitors. (See Table 4 in the ARISTADA full Prescribing Information.)

Commonly Observed Adverse Reactions: In pharmacokinetic studies the safety profile of ARISTADA INITIO was generally consistent with that observed for ARISTADA. The most common adverse reaction (≥5% incidence and at least twice the rate of placebo reported by patients treated with ARISTADA 441 mg and 882 mg monthly) was akathisia.

**Injection-Site Reactions:** In pharmacokinetic studies evaluating ARISTADA INITIO, the incidences of injectionsite reactions with ARISTADA INITIO were similar to the incidence observed with ARISTADA. Injection-site reactions were reported by 4%, 5%, and 2% of patients treated with 441 mg ARISTADA (monthly), 882 mg ARISTADA (monthly), and placebo, respectively. Most of these were injection-site pain and associated with the first injection and decreased with each subsequent injection. Other injection-site reactions (induration, swelling, and redness) occurred at less than 1%.

**Dystonia:** Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first days of treatment and at low doses.

**Pregnancy/Nursing:** May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure. Advise patients to notify their healthcare provider of a known or suspected pregnancy. Inform patients that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ARISTADA INITIO and/or ARISTADA during pregnancy. Aripiprazole is present in human breast milk. The benefits of breastfeeding should be considered along with the mother's clinical need for ARISTADA INITIO and/or ARISTADA and any potential adverse effects on the infant from ARISTADA INITIO and/or ARISTADA or from the underlying maternal condition.

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**ARISTADA** aripiprazole lauroxil

extended-release injectable suspension



441 mg 662 mg 882 mg 1064 mg

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INITIO®
aripiprazole lauroxil
extended-release injectable suspension

675 mg



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# **NOTES**





# **NOTES**





### For additional information:



or



Please see additional Important Safety Information on pages 38 to 39 and accompanying full Prescribing Information, including Boxed Warning, for ARISTADA INITIO and ARISTADA.



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