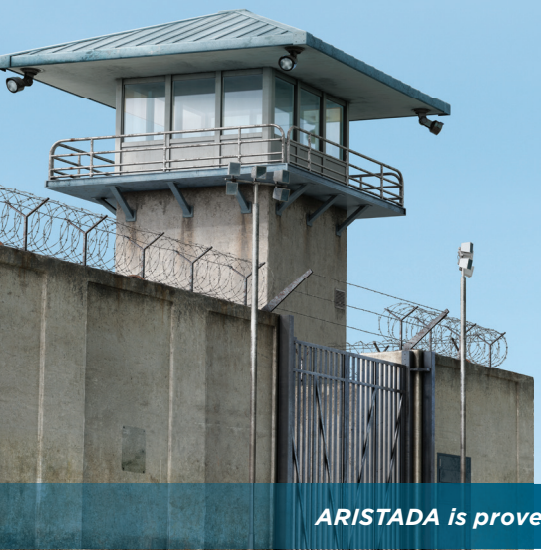


For justice-involved people with schizophrenia

TRANSITION

ARISTADA is proven effective for schizophrenia in adults

Learn more at aristadahcp.com

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 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.

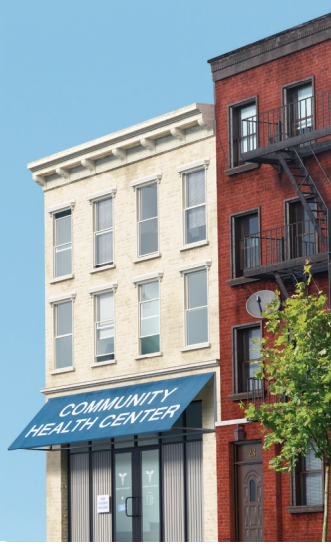
Tardive Dyskinesia (TD): The risk of developing TD (a syndrome of abnormal, involuntary movements) and the potential for it to become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic increase. The syndrome can develop, although much less 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.

OF CARE TAKES TIME



FULLY DOSE ON DAY 1 FOR 2 MONTHS OF TREATMENT

Initiate treatment* on day 1 with one ARISTADA INITIO® (aripiprazole lauroxil) injection, a single 30 mg dose of oral aripiprazole, and the first dose of ARISTADA® (aripiprazole lauroxil) 1064 mg.[1,2]

*Establish tolerability with oral aripiprazole prior to initiating ARISTADA or ARISTADA INITIO.[1,2]

Please see the full Prescribing Information for ARISTADA INITIO and ARISTADA for more information on dosage and administration.

IMPORTANT SAFETY INFORMATION FOR ARISTADA INITIO AND ARISTADA *(continued)*

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 and ARISTADA 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 injection-site 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.

Please see Brief Summaries of full Prescribing Information, including Boxed Warning, for ARISTADA INITIO and ARISTADA on the following pages.

References: 1. ARISTADA INITIO [package insert]. Waltham, MA: Alkermes, Inc; 2018.
2. ARISTADA [package insert]. Waltham, MA: Alkermes, Inc; 2018.

ARISTADA INITIO® aripiprazole lauroxil extended-release injectable suspension
675 mg

+

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

ARISTADA INITIO™ (aripiprazole lauroxil) extended-release injectable suspension, for intramuscular use

BRIEF SUMMARY OF PRESCRIBING INFORMATION

(For complete details, please see full Prescribing Information and Medication Guide.)

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 is not approved for the treatment of patients with dementia-related psychosis**

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

CONTRAINDICATIONS: ARISTADA INITIO is contraindicated in patients with a known hypersensitivity reaction to aripiprazole. Hypersensitivity reactions have ranged from pruritus/urticaria to anaphylaxis.

WARNINGS AND PRECAUTIONS

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 is 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 is 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 only. 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. 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.

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 antipsychotics, consider discontinuation of the antipsychotic drug. However, some patients may require antipsychotic treatment 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.

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 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, monitor orthostatic vital signs.

Falls: Antipsychotics including ARISTADA INITIO 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 $<1000/mm^3$) and follow their WBC until recovery.

Seizures: As with other antipsychotic drugs, use ARISTADA INITIO 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, 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 INITIO 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 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 other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

ADVERSE REACTIONS

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.

The safety of ARISTADA INITIO, in combination with oral aripiprazole, for the initiation of ARISTADA when used for the treatment of schizophrenia in adults has been established and is based on clinical trials of ARISTADA (aripiprazole lauroxil) including 1019 adult patients with schizophrenia.

Patient Exposure: ARISTADA INITIO has been evaluated for safety in 170 adult patients in clinical trials in schizophrenia.

In pharmacokinetic studies, the safety profile of ARISTADA INITIO was generally consistent with that observed for ARISTADA.

ARISTADA (Aripiprazole Lauroxil) Trials in Adults with Schizophrenia

Commonly Observed Adverse Reactions with Aripiprazole Lauroxil: The most common adverse reaction (incidence ≥5% and at least twice the rate of placebo in patients treated with aripiprazole lauroxil) was akathisia.

Adverse Reactions Occurring at an Incidence of 2% or More in Aripiprazole Lauroxil-Treated Patients: Adverse reactions associated with the use of aripiprazole lauroxil (incidence of 2% or greater, rounded to the nearest percent and aripiprazole lauroxil incidence greater than placebo) that occurred were: injection site pain, increased weight, increased blood creatinine phosphokinase, akathisia, headache, insomnia, and restlessness.

Injection Site Reactions

ARISTADA INITIO

In pharmacokinetic studies evaluating ARISTADA INITIO, the incidences of injection site reactions with ARISTADA INITIO were similar to the incidence observed with aripiprazole lauroxil.

ARISTADA (Aripiprazole Lauroxil)

Injection site reactions were reported by 4% of patients treated with 441 mg aripiprazole lauroxil and 5% of patients treated with 882 mg aripiprazole lauroxil compared to 2% of patients treated with placebo. Most of these were injection site pain (3%, 4% and 2% in the 441 mg aripiprazole lauroxil, 882 mg aripiprazole lauroxil and placebo groups, respectively). Other injection site reactions (induration, swelling and redness) occurred at less than 1%.

Extrapyramidal Symptoms: In a schizophrenia efficacy study in aripiprazole lauroxil-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 patients.

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 with Aripiprazole Lauroxil: 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
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 INITIO or aripiprazole lauroxil.

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, 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

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

DRUG INTERACTIONS

Table 1: Clinically Important Drug Interactions With ARISTADA INITIO

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 effect 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
Benzodiazepines	
Clinical Impact	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.
Intervention	Avoid concomitant use of ARISTADA INITIO with benzodiazepines because the dosage of ARISTADA INITIO cannot be modified.
Examples	lorazepam

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Exposure Registry: There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to ARISTADA INITIO 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 8 and 23 times, respectively, the maximum recommended human dose (MRHD) of 675 mg based on body surface area (mg/m^2). 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.

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 ARISTADA (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 1 to 8 times the MRHD of 675 mg based on mg/m^2, and at doses of 241, 723, and 2893 mg/animal in pregnant rabbits which are approximately 2 to 23 times the MRHD based on mg/m^2. 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 MRHD of 30 mg/day based

on mg/m^2 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 based on mg/m^2.

At 3 and 10 times the oral MRHD based on mg/m^2, 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 based on mg/m^2 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 based on mg/m^2 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 based on mg/m^2 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.

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

Pediatric Use: Safety and effectiveness of ARISTADA INITIO in pediatric patients have not been established.

Geriatric Use: Safety and effectiveness of ARISTADA INITIO 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 is not approved for the treatment of patients with dementia-related psychosis.

CYP2D6 Poor Metabolizers: 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 one strength in a single-dose pre-filled syringe).

Hepatic and Renal Impairment: No dosage adjustment for ARISTADA INITIO 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).

Other Specific Populations: No dosage adjustment for ARISTADA INITIO is required on the basis of a patient's sex, race, or smoking status.

OVERDOSAGE

Human Experience: 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.

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

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*.

PATIENT COUNSELING INFORMATION

Physicians are advised to discuss the FDA-approved patient labeling (Medication Guide) with patients for whom they prescribe ARISTADA INITIO.

This Brief Summary is based on ARISTADA INITIO Full Prescribing Information Rev June 2018.

Manufactured and marketed by Alkermes, Inc., Waltham, MA 02451-1420.

ARISTADA® (aripiprazole lauroxil) extended-release injectable suspension, for intramuscular use

BRIEF SUMMARY OF PRESCRIBING INFORMATION

(*For complete details, please see full Prescribing Information and Medication Guide.*)

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**

INDICATIONS AND USAGE: ARISTADA is an atypical antipsychotic indicated for the treatment of schizophrenia in adults.

CONTRAINDICATIONS: ARISTADA is contraindicated in patients with a known hypersensitivity reaction to aripiprazole. Hypersensitivity reactions have ranged from pruritus/urticaria to anaphylaxis.

WARNINGS AND PRECAUTIONS

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.

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.

Potential for Dosing and Medication Errors: Medication errors, including substitution and dispensing errors, between ARISTADA and ARISTADA INITIO® (aripiprazole lauroxil) could occur. ARISTADA INITIO is 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. 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.

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, 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.

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.

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 1.

Table 1: 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

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.

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 1 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. 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.

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.

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.

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.

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.

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).

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.

ADVERSE REACTIONS

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.

Patient Exposure: ARISTADA has been evaluated for safety in 1180 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 2.

Table 2: 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

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

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 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%. In an open-label pharmacokinetic study evaluating 441 mg monthly, 882 mg every 6 weeks, and 1064 mg every 2 months, injection-site reactions were similar across the dose groups.

Extrapyramidal Symptoms: In the 12-week schizophrenia efficacy study, 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 patients (Table 3).

Table 3: 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
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

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

DRUG INTERACTIONS

Drugs Having Clinically Important Interactions With ARISTADA

Table 4: Clinically Important Drug Interactions With ARISTADA

Strong CYP3A4 Inhibitors and CYP2D6 Inhibitors	
Clinical Impact:	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.
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 of 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 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.
Intervention:	Monitor sedation and blood pressure. Adjust dose accordingly.
Example:	lorazepam

USE IN SPECIFIC POPULATIONS

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 5 and 15 times, respectively, the maximum recommended human dose (MRHD) of 1064 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 0.6 to 5 times the maximum recommended human dose (MRHD) of 1064 mg ARISTADA on mg/m^2 basis and at doses of 241, 723, and 2893 mg/animal in pregnant rabbits which are approximately 1 to 15 times the MRHD on mg/m^2 basis. However, aripiprazole caused developmental toxicity and possible teratogenic effects in rats and rabbits.

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.

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.

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

Geriatric Use: Safety and effectiveness of 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 is not approved for treatment of patients with dementia-related psychosis.

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).

Other Specific Populations: No dosage adjustment for ARISTADA is required on the basis of a patient's sex, race, or smoking status.

OVERDOSAGE

Human Experience: 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.

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

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*.

PATIENT COUNSELING INFORMATION

Physicians are advised to discuss the FDA-approved patient labeling (Medication Guide) with patients for whom they prescribe ARISTADA.

This Brief Summary is based on ARISTADA Full Prescribing Information
Rev November 2018
Manufactured and marketed by Alkermes, Inc., Waltham, MA 02451-1420

EDITOR'S CHOICE | Psychiatric Services

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Lisa B. Dixon, M.D., M.P.H.

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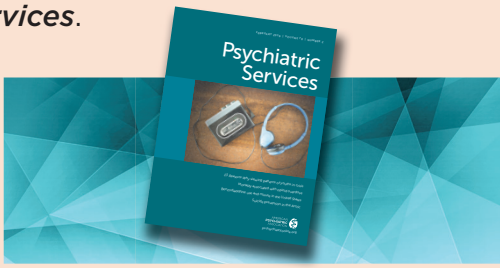

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