



## FDA Approves Two-Month ARISTADA® for Treatment of Schizophrenia

June 6, 2017

— First and Only Long-Acting Atypical Antipsychotic With Two-Month Dosing Option —

— Approval Expands ARISTADA's Product Offerings to Include Once-Monthly, Once-Every-Six-Weeks and Once-Every-Two-Months Dosing Durations —

DUBLIN--(BUSINESS WIRE)--Jun. 6, 2017-- [Alkermes plc](#) (NASDAQ: ALKS) today announced that the U.S. Food and Drug Administration (FDA) has approved two-month ARISTADA® (aripiprazole lauroxil) extended-release injectable suspension for the treatment of schizophrenia. ARISTADA is now FDA-approved in four doses and three dosing duration options (441 mg, 662 mg or 882 mg once monthly, 882 mg once every six weeks and 1064 mg once every two months) and can be initiated at any dose or interval, offering an unprecedented range of flexibility to patients and healthcare providers. The new two-month dose is expected to be available in mid-June.

"We designed ARISTADA to offer flexibility to meet the real-world needs of patients suffering from schizophrenia and the healthcare professionals providing their care. As the first and only long-acting atypical antipsychotic approved in three dosing durations and with the ability to initiate treatment at any dose or duration, ARISTADA provides a range of options to help clinicians tailor treatment to the individual needs of their patients," said Elliot Ehrich, M.D., Executive Vice President, Research and Development of Alkermes. "Building on nearly two decades of experience developing innovative medicines for chronic and serious CNS diseases, we are dedicated to helping improve the lives of patients with treatment options that are well-suited for use in today's complex treatment system."

Treatment adherence for patients on daily therapy for chronic diseases is a known challenge for patients, and schizophrenia may make this challenge even greater. Long-acting injectable medications, like ARISTADA, eliminate the burden of taking an oral antipsychotic medicine on a daily basis. The newly approved two-month ARISTADA gives people living with schizophrenia an option to treat their symptoms with only six injections per year.

"Transitioning patients with schizophrenia from inpatient care to outpatient settings can be challenging. The availability of an antipsychotic that can be initiated prior to hospital discharge and provide therapeutic levels of medication for two months will be a welcome new treatment option for healthcare providers, caregivers and patients," said Joseph McEvoy, M.D., I. Clark Case Distinguished Chair in Psychotic Disorders at Augusta University and Professor Emeritus of Psychiatry and Behavioral Health at Duke University Medical Center. "The clinical community is increasingly using long-acting atypical antipsychotic medications earlier in the treatment paradigm as recognition grows of the benefits of less frequent dosing and the resulting ability to focus on other important treatment goals for patients."

### **About Schizophrenia**

Schizophrenia is a chronic, severe and disabling brain disorder. The disease is marked by positive symptoms (hallucinations and delusions) and negative symptoms (depression, blunted emotions and social withdrawal), as well as by disorganized thinking. An estimated 2.4 million American adults have schizophrenia,<sup>1</sup> with men and women affected equally.

### **About ARISTADA®**

ARISTADA is an injectable atypical antipsychotic with one-month, six-week and two-month dosing options for the treatment of schizophrenia. ARISTADA is administered by a healthcare professional. Once in the body, ARISTADA converts to aripiprazole. ARISTADA was originally approved by the FDA in October 2015.

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

#### **INDICATION**

ARISTADA is indicated for the treatment of schizophrenia.

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

**Neuroleptic Malignant Syndrome (NMS):** A potentially fatal symptom complex sometimes referred to as NMS may occur with administration of antipsychotic drugs, including 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

creatin 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 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 ARISTADA if a patient develops such urges.

**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 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. Patients with a history of clinically significant low white blood cell count (WBC)/absolute neutrophil count (ANC) and history of drug-induced leukopenia/neutropenia should have frequent complete blood count (CBC) during the first few months of receiving ARISTADA. Consider discontinuation of ARISTADA at the first sign of a clinically significant decline in WBC count 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  $<1000/\text{mm}^3$ ) and follow their WBC until recovery.

**Seizures:** ARISTADA should be used with caution in patients with a history of seizures or with conditions that lower the seizure threshold.

**Potential for Cognitive and Motor Impairment:** ARISTADA may impair judgment, thinking, or motor skills. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are certain 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:** Decreasing the ARISTADA dosage is recommended in patients taking strong CYP3A4 inhibitors and/or strong CYP2D6 inhibitors for longer than 2 weeks. Increasing the ARISTADA dosage from 441 mg to 662 mg is recommended in patients taking CYP3A4 inducers for longer than 2 weeks. No ARISTADA dosage changes are recommended for patients taking CYP450 modulators for less than 2 weeks.

**Most Commonly Observed Adverse Reaction:** The most common adverse reaction ( $\geq 5\%$  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:** 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 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 and any potential adverse effects on the infant from ARISTADA or from the underlying maternal condition.

Please see [FULL PRESCRIBING INFORMATION](#), including **Boxed Warning**, for ARISTADA.

### **About Alkermes**

Alkermes plc is a fully integrated, global biopharmaceutical company developing innovative medicines for the treatment of central nervous system (CNS) diseases. The company has a diversified commercial product portfolio and a substantial clinical pipeline of product candidates for chronic diseases that include schizophrenia, depression, addiction and multiple sclerosis. Headquartered in Dublin, Ireland, Alkermes plc has an R&D center in Waltham, Massachusetts; a research and manufacturing facility in Athlone, Ireland; and a manufacturing facility in Wilmington, Ohio. For more information, please visit Alkermes' website at [www.alkermes.com](http://www.alkermes.com).

### **Note Regarding Forward-Looking Statements**

Certain statements set forth in this press release constitute "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including, but not limited to, statements concerning the timing of the launch of two-month ARISTADA in the U.S., the commercialization of two-month ARISTADA and the potential therapeutic and commercial value of two-month ARISTADA for the treatment of schizophrenia. The company cautions that forward-looking statements are inherently uncertain. Although the company believes that such statements are based on reasonable assumptions within the bounds of its knowledge of its business and operations, the forward-looking statements are neither promises nor guarantees and they are necessarily subject to a high degree of uncertainty and risk. Actual performance and results may differ materially from those expressed or implied in the forward-looking statements due to various risks and uncertainties. These risks and uncertainties include, among others: when two-month ARISTADA will become commercially available; whether the safety results demonstrated in our open-label pharmacokinetic, safety and tolerability study of two-month ARISTADA for the treatment of schizophrenia will be predictive of results when commercialized; whether two-month ARISTADA will be commercialized successfully; whether third party payers will cover or reimburse the two-month dosing option of ARISTADA for the treatment of schizophrenia; and those risks and uncertainties described under the heading "Risk Factors" in the company's Annual Report on Form 10-K for the year ended Dec. 31, 2016 and Quarterly Report on Form 10-Q for the quarter ended Mar. 31, 2017 and in subsequent filings made by the company with the U.S. Securities and Exchange Commission (SEC), which are available on the SEC's website at [www.sec.gov](http://www.sec.gov). Existing and prospective investors are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date hereof. Except as required by law, the company disclaims any intention or responsibility for updating or revising any forward-looking statements contained in this press release.

ARISTADA<sup>®</sup> is a registered trademark of Alkermes Pharma Ireland Limited.

<sup>1</sup>National Institutes of Health. *Schizophrenia*. Accessed on June 5, 2017 from <https://report.nih.gov/nihfactsheets/ViewFactSheet.aspx?csid=67>.



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