FDA Approves ARISTADA INITIO™ for the Initiation of ARISTADA® for Schizophrenia

July 2, 2018

-- Novel Regimen Enables Physicians to Fully Dose Up to Two Months of ARISTADA Treatment on Day One --

DUBLIN, July 2, 2018 /PRNewswire/ -- Alkermes plc (Nasdaq: ALKS) today announced that the U.S. Food and Drug Administration (FDA) has approved ARISTADA INITIO ™ (aripiprazole lauroxil) for the initiation of ARISTADA® (aripiprazole lauroxil), a long-acting injectable atypical antipsychotic for the treatment of schizophrenia in adults. For the first time, ARISTADA INITIO, in combination with a single 30 mg dose of oral aripiprazole, provides physicians with an alternative regimen to initiate patients onto any dose of ARISTADA on day one. ARISTADA INITIO is expected to be available in mid-July.

For people living with schizophrenia, medication compliance and continuity of care can be challenging and the transition from inpatient care to outpatient settings can be an especially vulnerable time.[1] Previously, the standard initiation regimen for ARISTADA included 21 consecutive days of oral aripiprazole starting with the first ARISTADA dose. The ARISTADA INITIO regimen provides patients with relevant levels of aripiprazole within four days of initiation. The result is an alternative initiation regimen that gives healthcare providers an additional tool to support patients during this critical time in their treatment journey.

"The approval of ARISTADA INITIO makes ARISTADA the first and only long-acting atypical antipsychotic that can be initiated on day one, representing an important addition to the treatment paradigm for the complex illness of schizophrenia," said David Walling, Ph.D., Chief Executive Officer and Principal Investigator of the Collaborative Neuroscience Network. "For physicians and caregivers alike, the ARISTADA INITIO regimen provides a level of confidence that patients can walk out the door with up to two months of coverage with a proven medication in their system. This supports continuity of care for patients and allows the care team to focus their efforts on other aspects of the treatment paradigm that contribute to long-term positive outcomes."

ARISTADA and ARISTADA INITIO both contain aripiprazole lauroxil; however, the two medications are not interchangeable because of differing pharmacokinetic profiles. ARISTADA INITIO leverages the company's proprietary NanoCrystal® technology and is designed to provide an extended-release formulation using a smaller particle size of aripiprazole lauroxil compared to ARISTADA, thereby enabling faster dissolution and leading to more rapid achievement of relevant levels of aripiprazole.

ARISTADA INITIO can be used for initiation onto any dose of ARISTADA (441 mg, 662 mg or 882 mg monthly, 882 mg once every six weeks and 1064 mg once every two months), offering a wide range of flexible dosing options for patients and healthcare providers. The first ARISTADA dose may be administered on the same day as ARISTADA INITIO or up to 10 days thereafter.

"Long-acting injectable atypical antipsychotics have an increasingly recognized role in the treatment of schizophrenia. The ability to initiate ARISTADA on day one may be particularly useful in the hospital setting, where more than one-third of patients initiate onto long-acting therapies," said Craig Hopkinson, M.D., Chief Medical Officer and Senior Vice President of Medicines Development and Medical Affairs at Alkermes. "The approval of ARISTADA INITIO adds an important new option to our growing schizophrenia portfolio and reaffirms Alkermes' commitment to developing innovative treatments that address the real-world needs of people living with schizophrenia."

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 live with schizophrenia,[2] with men and women affected equally.

About ARISTADA INITIO ™

ARISTADA INITIO, in combination with a single 30 mg dose of oral aripiprazole, can be used to initiate onto any dose of ARISTADA. The first ARISTADA dose may be administered on the same day as ARISTADA INITIO or up to 10 days thereafter.

About ARISTADA®

ARISTADA is an injectable atypical antipsychotic approved in four doses and three dosing durations for the treatment of schizophrenia (441 mg, 662 mg or 882 mg monthly, 882 mg once every six weeks and 1064 mg once every two months). Once in the body, ARISTADA converts to aripiprazole.

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.

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 only. 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.

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 CYP3A4 inhibitors, CYP2D6 inhibitors, or 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 full Prescribing Information, including Boxed Warning for ARISTADA INITIO and ARISTADA.

About Alkermes plc

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.

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 commercial launch of ARISTADA INITIO in the U.S., the commercialization of ARISTADA INITIO and the potential therapeutic and commercial value of ARISTADA INITIO for initiation of 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 ARISTADA INITIO will become commercially available; whether the pharmacokinetic and safety results demonstrated in the company's open-label pharmacokinetic, safety and tolerability study of ARISTADA INITIO for initiation of ARISTADA for the treatment of schizophrenia will be predictive of results when commercialized; whether ARISTADA INITIO will be commercialized successfully; whether third-party payers will cover or reimburse ARISTADA INITIO for initiation 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, 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. 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.

[1] Markowitz, M., et al. (2013). "Antipsychotic adherence patterns and health care utilization and costs among patients discharged after a schizophrenia-related hospitalization." *BMC Psychiatry* 13(1): 246.

[2] National Institutes of Health. *Schizophrenia*. Accessed on June 30, 2018 from https://report.nih.gov/nihfactsheets/ViewFactSheet.aspx?csid=67.

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