Alkermes Announces FDA Approval of LYBALVI™ for the Treatment of Schizophrenia and Bipolar I Disorder

June 1, 2021

-- New Oral Medication Offers Established Antipsychotic Efficacy of Olanzapine With Less Weight Gain --
-- Commercial Launch Planned for Fourth Quarter 2021 --
-- Company to Host Investor Conference Call Today at 8:30 a.m. ET --

DUBLIN, June 1, 2021 /PRNewswire/ -- Alkermes plc (Nasdaq: ALKS) today announced that the U.S. Food and Drug Administration (FDA) has approved LYBALVI™ (olanzapine and samidorphan) for the treatment of adults with schizophrenia and for the treatment of adults with bipolar I disorder, as a maintenance monotherapy or for the acute treatment of manic or mixed episodes, as monotherapy or an adjunct to lithium or valproate. LYBALVI is a once-daily, oral atypical antipsychotic composed of olanzapine, an established antipsychotic agent, and samidorphan, a new chemical entity.

"Schizophrenia and bipolar I disorder are complex, chronic diseases and there remains a persistent need for new medications with proven efficacy and safety. Olanzapine, a highly-efficacious atypical antipsychotic, is associated with significant side effects, including weight gain, that may impact patients' treatment experiences and limit its use," said René S. Kahn, M.D., Ph.D., Esther and Joseph Klingenstein Professor & Chair, Department of Psychiatry and Behavioral Health System at the Icahn School of Medicine at Mount Sinai. "With the efficacy of olanzapine and evidence of less weight gain in patients with schizophrenia, LYBALVI brings a welcome new addition to our medication arsenal."

"LYBALVI represents an important new treatment option for adults with schizophrenia or bipolar I disorder, their clinicians and caregivers, and reflects Alkermes' commitment to developing new therapies that support patient-centered care," said Richard Pops, Chairman and Chief Executive Officer at Alkermes. "We share this accomplishment with our employees and the many researchers, advocates, clinicians and patients who have been essential to the LYBALVI development program since its inception. Our existing commercial capabilities and presence in the antipsychotic market with ARISTADA® provide an important foundation for the commercialization of LYBALVI, and we look forward to making this new medicine available to patients and clinicians later this year."

In the ENLIGHTEN clinical development program, LYBALVI demonstrated antipsychotic efficacy, safety and tolerability, including statistically significantly less weight gain than olanzapine in patients with schizophrenia in the ENLIGHTEN-2 study. Results from the ENLIGHTEN program's pivotal ENLIGHTEN-1 efficacy study and ENLIGHTEN-2 weight study have been published in peer-reviewed journals[1,2] and are included in the approved labeling for LYBALVI. The FDA approved LYBALVI under the 505(b)(2) regulatory pathway based on data from 27 clinical studies, including 18 studies evaluating LYBALVI and nine studies evaluating samidorphan alone, and the FDA's findings of safety and effectiveness of olanzapine in the treatment of bipolar I disorder and schizophrenia. Data suggest that olanzapine-associated weight gain is disease independent.[3]

"People living with schizophrenia or bipolar I disorder must evaluate both efficacy and tolerability when making treatment decisions," said Paul Gionfriddo, President and CEO of Mental Health America (MHA). "We are grateful that companies like Alkermes are driven to continue developing new treatment options in psychiatry that seek to address unmet needs of our community and we applaud the FDA for considering the experiences of individuals living with these conditions."

Alkermes expects to make LYBALVI available for patients in the fourth quarter of 2021.

Conference Call
Alkermes will host a conference call for analysts and investors on Tuesday, June 1, 2021 at 8:30 a.m. ET (1:30 p.m. BST). The webcast may be accessed on the Investors section of Alkermes' website at www.alkermes.com. To participate in the question and answer session, please dial in to the conference call, which may be accessed by dialing +1 877-407-2988 for U.S. callers and +1 201-389-0923 for international callers. In addition, a replay of the conference call may be accessed by visiting Alkermes' website or by dialing +1 877-660-6853 for U.S. callers and +1 201-612-7415 for international callers, using replay access code 13719944. The conference call replay will be available from 11:30 a.m. ET (4:30 p.m. BST) on Tuesday, June 1, 2021, through Tuesday, June 8, 2021.

About Schizophrenia
Schizophrenia is a serious brain disorder marked by positive symptoms (hallucinations and delusions, disorganized speech and thoughts, and agitated or repeated movements) and negative symptoms (depression, blunted emotions and social withdrawal).[4] Schizophrenia affects approximately 1.1% of the U.S. population.[5]

About Bipolar I Disorder
Bipolar disorder is a brain disorder that is marked by extreme changes in a person's mood, energy and ability to function. Individuals with this brain disorder may experience debilitating changes in mood from extreme highs (mania) to extreme lows (depression). Bipolar I disorder is characterized by the occurrence of at least one manic episode, with or without the occurrence of a major depressive episode, and affects approximately one percent of the adult population in the United States in any given year.[6]

About the ENLIGHTEN Clinical Development Program
The ENLIGHTEN clinical development program for LYBALVI includes two key studies in patients with schizophrenia: ENLIGHTEN-1 and ENLIGHTEN-2.

ENLIGHTEN-1 evaluated the antipsychotic efficacy, safety and tolerability of LYBALVI compared to placebo over four weeks in 403 patients experiencing an acute exacerbation of schizophrenia. This study met its prespecified primary endpoint, with LYBALVI demonstrating statistically significant reductions from baseline in Positive and Negative Syndrome Scale (PANSS) scores compared to placebo ($p<0.001$). An olanzapine comparator arm was also included, which achieved similar improvements from baseline PANSS scores compared to placebo ($p=0.004$). The most common adverse events (AEs) for both the LYBALVI and olanzapine treatment groups were weight gain, somnolence and dry mouth.

ENLIGHTEN-2 evaluated the weight gain profile of LYBALVI compared to olanzapine over six months in 561 patients with stable schizophrenia. This study met its prespecified co-primary endpoints, demonstrating both a lower mean percent weight gain from baseline at six months compared to the olanzapine group ($p=0.003$) and a lower proportion of patients who gained 10% or more of their baseline body weight at six months compared to the olanzapine group ($p=0.003$). The most common AEs reported in the LYBALVI treatment group were weight gain, somnolence and dry mouth; the most common AEs reported in the olanzapine treatment group were weight gain, somnolence and increased appetite.

The program also included supportive studies to evaluate the pharmacokinetic and metabolic profile and long-term safety of LYBALVI, and pharmacokinetic bridging studies comparing LYBALVI and ZYPREXA® (olanzapine).

About LYBALVI™ (olanzapine and samidorphan)
LYBALVI (olanzapine and samidorphan) is a once-daily, oral atypical antipsychotic drug for the treatment of adults with schizophrenia and for the treatment of adults with bipolar I disorder, as a maintenance monotherapy or for the acute treatment of manic or mixed episodes, as monotherapy or an adjunct to lithium or valproate. LYBALVI is composed of olanzapine, an established antipsychotic agent, co-formulated with samidorphan, a new chemical entity, in a single bilayer tablet. LYBALVI will be available in fixed dosage strengths composed of 10 mg of samidorphan and 5 mg, 10 mg, 15 mg or 20 mg of olanzapine.

INDICATIONS and IMPORTANT SAFETY INFORMATION FOR LYBALVI™ (olanzapine and samidorphan)

INDICATIONS
LYBALVI is indicated for the treatment of:

- Schizophrenia in adults
- Bipolar I disorder in adults
  - Acute treatment of manic or mixed episodes as monotherapy and as adjunct to lithium or valproate
  - Maintenance monotherapy treatment

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

Contraindications: LYBALVI is contraindicated in patients:

- Who are using opioids
- Who are undergoing acute opioid withdrawal

If LYBALVI is administered with lithium or valproate, refer to the lithium or valproate Prescribing Information for the contraindications for these products.

Cerebrovascular Adverse Reactions, Including Stroke in Elderly Patients with Dementia-Related Psychosis: Cerebrovascular adverse reactions (e.g., stroke, transient ischemic attack), including fatalities, were reported in patients in trials of olanzapine in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse reactions in patients treated with olanzapine compared to patients treated with placebo. LYBALVI is not approved for the treatment of patients with dementia-related psychosis.

Precipitation of Severe Opioid Withdrawal in Patients who are Physiologically Dependent on Opioids: Samidorphan, an opioid antagonist that is a component of LYBALVI, can precipitate opioid withdrawal in patients who are dependent on opioids, which can lead to an opioid withdrawal syndrome, sometimes requiring hospitalization. Therefore, LYBALVI is contraindicated in patients who are using opioids or undergoing acute opioid withdrawal. Prior to initiating LYBALVI, there should be at least a 7-day opioid-free interval from last use of short-acting opioids, and at least a 14-day opioid-free interval from the last use of long-acting opioids.

Vulnerability to Life-Threatening Opioid Overdose:
Risk of Opioid Overdose from Attempts to Overcome Samidorphan Blockade
Attempting to overcome LYBALVI's opioid blockade with high or repeated doses of exogenous opioids could lead to life-threatening or fatal opioid intoxication (e.g., respiratory arrest, circulatory collapse), particularly if LYBALVI therapy is interrupted or discontinued subjecting the patient to high levels of unopposed opioid agonist as the samidorphan blockade wanes.

In emergency situations, if a LYBALVI-treated patient requires opioid treatment as part of anesthesia or analgesia, discontinue LYBALVI. Opioids should be administered by properly trained individual(s) and patient should be continuously monitored in a setting equipped and staffed for cardiopulmonary resuscitation.

Risk of Resuming Opioids in Patients with Prior Opioid Use
Patients with a history of chronic opioid use prior to treatment with LYBALVI may have decreased opioid tolerance if LYBALVI therapy is interrupted or discontinued.

Neuroleptic Malignant Syndrome (NMS): NMS, a potentially fatal symptom complex, has been reported with administration of antipsychotic drugs. NMS may cause hyperpyrexia, muscle rigidity, delirium, and autonomic instability. Additional signs may include elevated creatine phosphokinase,

myoglobinuria (rhabdomyolysis), and acute renal failure. If NMS is suspected, immediately discontinue LYBALVI and provide intensive symptomatic treatment and monitoring.

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): A potentially fatal condition, DRESS has been reported with exposure to olanzapine, a component of LYBALVI. Symptoms include a cutaneous reaction (such as rash or exfoliative dermatitis), eosinophilia, fever, and/or lymphadenopathy with systemic complications such as hepatitis, nephritis, pneumonitis, myocarditis, and/or pericarditis. If DRESS is suspected, discontinue LYBALVI.

Metabolic Changes: Atypical antipsychotic drugs have been associated with metabolic changes including:
Hyperglycemia and 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.
Dyslipidemia: Antipsychotics have caused adverse alterations in lipids.
Weight gain: Weight gain has been observed with use of antipsychotics.
Assess fasting glucose and lipids when initiating LYBALVI and monitor periodically. Monitor weight at baseline and frequently thereafter.

Tardive Dyskinesia (TD): Risk of developing TD (a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements) and the likelihood that it will become irreversible increases with duration of treatment and the cumulative dose. The risk appears to be highest among the elderly, especially elderly women, but it is not possible to predict which patients are likely to develop TD. The syndrome can develop after a relatively brief treatment period, even at low doses, or after treatment discontinuation. LYBALVI should be prescribed in a manner that most likely reduces the risk of TD.

For chronic treatment, use the lowest dose and the shortest duration of treatment producing a satisfactory clinical response. If signs and symptoms of TD appear, drug discontinuation should be considered.

Orthostatic Hypotension and Syncope: Atypical antipsychotics cause orthostatic hypotension and syncope. The risk is greatest during initial dose titration and when increasing the dose. Monitor orthostatic vital signs in patients who are vulnerable to hypotension, patients with known cardiovascular disease, and patients with cerebrovascular disease.

Falls: LYBALVI may cause somnolence, postural hypotension, and motor and sensory instability, which may lead to falls and, consequently, fractures or other injuries. Complete fall risk assessment upon initiating treatment and recurrently for patients with diseases, conditions, or medications that could exacerbate these effects.

Leukopenia, Neutropenia, and Agranulocytosis: Leukopenia and neutropenia have been reported during treatment with antipsychotics, including LYBALVI. Agranulocytosis (including fatal cases) has been reported with other agents in this class. Monitor patients with a history of significantly low white blood count (WBC) or absolute neutrophil count (ANC) or drug-induced leukopenia/neutropenia; perform a complete blood cell count (CBC) frequently during the first few months of therapy. Discontinue LYBALVI at the first sign of a clinically significant decline in WBC and in patients with severe neutropenia.

Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use, including LYBALVI. Use caution in patients at risk for aspiration.

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

Potential for Cognitive and Motor Impairment: LYBALVI may cause somnolence, impair judgment, thinking, or motor skills. Patients should be cautioned about operating hazardous machinery, including motor vehicles, until they are certain that LYBALVI does not affect them adversely.

Body Temperature Dysregulation: Atypical antipsychotics may disrupt the body's ability to reduce core body temperature. Use LYBALVI with caution in patients who may exercise strenuously, may be exposed to extreme heat, receive concomitant medication with anticholinergic activity, or are subject to dehydration.

Anticholinergic (Antimuscarinic) Effects: Olanzapine, a component of LYBALVI, was associated with constipation, dry mouth, and tachycardia, all adverse reactions possibly related to cholinergic antagonism. Use LYBALVI with caution in patients with a current diagnosis or prior history of urinary retention, clinically significant prostatic hypertrophy, constipation, or a history of paralytic ileus or related conditions. The risk for severe adverse reactions (including fatalities) was increased with concomitant use of anticholinergic medications.

Hyperprolactinemia: As with other drugs that antagonize dopamine D2 receptors, olanzapine, a component of LYBALVI, elevates prolactin levels. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density.

Risks Associated with Combination Treatment with Lithium or Valproate: If LYBALVI is administered with lithium or valproate, refer to the lithium or valproate Prescribing Information for a description of the risks for these products including, but not limited to, the warnings and precautions for lithium or valproate.

ADVERSE REACTIONS
Most common adverse reactions (incidence ≥5% and at least twice that of placebo) were:
Schizophrenia (LYBALVI): weight increased, somnolence, dry mouth, and headache
Bipolar I Disorder, Manic or Mixed Episodes (olanzapine): asthenia, dry mouth, constipation, increased appetite, somnolence, dizziness, tremor
Bipolar I Disorder, Manic or Mixed Episodes, adjunct to Lithium or Valproate (olanzapine): dry mouth, dyspepsia, weight gain, increased appetite, dizziness, back pain, constipation, speech disorder, increased salivation, amnesia, paresthesia

Concomitant Medication: Concomitant use of LYBALVI is not recommended with strong CYP3A4 inducers, levodopa and dopamine agonists, and opioid agonists. Consider dosage reduction of olanzapine component of LYBALVI when using with strong CYP1A2 inhibitors. Consider dosage increase of olanzapine component of LYBALVI with CYP1A2 inducers. Use caution with diazepam, alcohol, other CNS acting drugs, or in patients receiving medication having anticholinergic (antimuscarinic) effects.

Monitor blood pressure and reduce dosage of antihypertensive drug in accordance with its approved product labeling.

Pregnancy: May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure. Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during treatment with LYBALVI. Inform that there is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to LYBALVI during pregnancy.

To report SUSPECTED ADVERSE REACTIONS, contact Alkermes at 1-888-235-8008 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see accompanying full Prescribing Information, including Boxed Warning, for LYBALVI.

About Alkermes plc

Alkermes plc is a fully-integrated, global biopharmaceutical company developing innovative medicines in the fields of neuroscience and oncology. The company has a portfolio of proprietary commercial products focused on addiction, schizophrenia and bipolar I disorder, and a pipeline of product candidates in development for neurodegenerative disorders and cancer. 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 potential therapeutic and commercial value of LYBALVI for the treatment of adults with schizophrenia and the treatment of adults with bipolar I disorder; the company's expectations regarding commercial activities, including the company's ability to leverage its existing commercial capabilities for the commercialization of LYBALVI and timing of when the company expects to make LYBALVI available for patients. 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: whether the clinical results for LYBALVI will be predictive of real-world results; unexpected costs or delays in the commercial launch of LYBALVI; whether LYBALVI will be commercialized successfully; whether third party payers will cover or reimburse LYBALVI for the treatment of adults with schizophrenia and the treatment of adults with bipolar I disorder; unanticipated impacts of the COVID-19 pandemic on the operations of the company; potential changes in the cost, scope and duration of the LYBALVI development and regulatory program; whether LYBALVI could be shown to be ineffective or unsafe; 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, 2020 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.

LYBALVI™ is a trademark, and ARISTADA® is a registered trademark, of Alkermes Pharma Ireland Limited. ZYPREXA® is a registered trademark of Eli Lilly & Company.

[1] Potkin et al. Efficacy and Safety of a Combination of Olanzapine and Samidorphan in Adult Patients With an Acute Exacerbation of Schizophrenia: Outcomes From the Randomized, Phase 3 ENLIGHTEN-1 Study. *J Clin Psych*, 2020;81(2):19m12769. https://doi.org/10.4088/JCP.19m12769

[2] Correll et al. Effects of Olanzapine Combined With Samidorphan on Weight Gain in Schizophrenia: A 24-Week Phase 3 Study. *Am J Psychiatry*, 2020;(177)12:1168-1178. https://doi.org/10.1176/appi.ajp.2020.19121279

[3] Zyprexa US Prescribing Information. Indianapolis, IN: Eli Lilly and Company. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/020592s074,021086s048,021253s061lbl.pdf

[4] American Psychiatric Association. Schizophrenia Spectrum and Other Psychiatric Disorders. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Washington, DC: American Psychiatric Publishing; 2013.

[5] Cloutier M. Journal of Clinical Psychiatry. 2016 Jun; 77(6): 764-71. https://www.psychiatrist.com/jcp/schizophrenia/economic-burden-schizophrenia-united-states-2013/

[6] Merikangas et al. Lifetime and 12-Month Prevalence of Bipolar Spectrum Disorder in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*, 2007 May; 64(5): 543-552. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1931566/

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